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NON-SPECIFIC ENTEROCOLITIS[1]

By W. T. COOKE and B. N. BROOKE

(From the Departments of Medicine and Surgery, The Queen Elizabeth Hospital, Birmingham)

With Plates 1 to 3

Apart from malignant lesions, the intestinal tract, though subject to attack from numerous causes, shows little variation in its pathological appearances to the naked eye. The inflammatory response to trauma or infection can produce mucosal ulceration, thickening of the bowel wall, and fistula formation, either singly or together. Difficulty therefore lies both in definition of the various diseases which afflict the intestines and in their aetiology, unless a definite organism can be found such as an anaerobic clostridium (Hobbs, Smith, Oakley, Warrack, and Cruikshank, 1953), a staphylococcus (Dack, 1943), or a member of the enteric or dysenteric groups. It is the purpose of the present paper to discuss a condition which appears to have no infective cause, which affects both small and large intestine, and which shows certain differences from the chronic cicatrizing lesions associated with the name of Crohn (1949) and from classical ulcerative colitis.

This condition of ileocolitis or enterocolitis is not new, and doubtless has been seen by many doctors, but in the past it has been regarded as a variant of some other disease, most commonly regional ileitis or ulcerative colitis. In their classical account of regional ileitis, Crohn, Ginzburg, and Oppenheimer (1932) drew attention to the similarity of symptoms in some cases of regional ileitis to those of ulcerative colitis. Although at first Crohn believed that regional ileitis stopped short at the ileocaecal valve, Colp (1934) and Mixter (1935) reported involvement of the sigmoid in regional ileitis. Moreover Crohn and Rosenak (1936) found nine such patients in whom simultaneous involvement of the small intestine and colon was noted; stress was laid on the chronic fibrotic and stenotic nature of the lesion in the small intestine. Further reports, such as those by Pugh (1945), Pemberton and Brown (1937), and Clark and Dixon (1939), have suggested that the site of the initial lesion in such patients is the small intestine, and that the colon is secondarily involved. In addition to this group of chronic ileocolitis, more acute and widespread disorders have been recognized in which the duodenum and ileum are involved in a non-specific granulomatous process of variable prognosis; occasionally this process has extended throughout the length of the intestinal canal, and the lesion in the colon has resembled ulcerative colitis (Olsan and Sussman, 1948). Pseudo-membranous colitis has also been described; in this condition the superficial

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mucosa of the whole intestinal tract may be involved (Kleckner, Bargen, and Baggenstoss, 1952). Similar conditions, often more acute, have also been seen after operation (Penner and Druckerman, 1948; Terplan, Paine, Sheffer, Egan, and Lansky, 1953) and after the administration of antibiotics (Reiner, Schlesinger, and Miller, 1952; Hansbro and Ferrell, 1953). On the other hand classical ulcerative colitis, which usually affects most severely the descending colon and sigmoid, involves the terminal ileum in some patients as a 'wash-back' phenomenon (Crohn, 1949; Warren and Sommers, 1949; Brooke, 1954).

In this clinic, from the medical point of view, patients have been encountered in whom the clinical picture was that of idiopathic steatorrhoea, but in whom radiological examination revealed evidence of colitis. From the surgical approach it has not been easy to reconcile what has been termed 'right-sided' colitis (Crohn and Berg, 1938; Crohn, Garlock, and Yarnis, 1947) with the more usual form of idiopathic ulcerative colitis. It is these two incompatibilities which have led us to suspect that there may be a separate condition of enterocolitis, and to analyse our personal experiences of 16 patients (nine men and seven women) in whom functional involvement of both small and large intestine has been manifest. The average daily excretion of more than 6 gm. of fat by a patient receiving 50 gm. of fat daily has been taken as evidence of disordered function of the small intestine, while evidence of colonic involvement has been provided by radiological examination or sigmoidoscopy. Furthermore, patients who showed definite evidence of a stenotic lesion of the small and large intestine, justifying the frank diagnosis of regional ileitis or colitis, have not been considered, although patients in whom the differentiation is still difficult have been brought into discussion.

Symptoms and Signs

Clinical descriptions of certain of these patients have already been published (Brooke and Cooke, 1951; Cooke, 1952; Brooke, 1953, 1954) in which reference was made to the different degrees of clinical severity of the disorder, mild, moderate, or fulminating; both the severity and the duration of the condition have differed from case to case, rendering the clinical picture variable and difficult to define. In all cases the presenting feature has been diarrhoea. There is a group of patients in whom the nature of the diarrhoea has appeared to be significant, being continuous over many years with four to eight motions daily, without the remissions or exacerbations characteristic of ulcerative colitis. The stools of these patients have not resembled those passed in ulcerative colitis, since blood and pus have not been predominant; indeed, although blood-cells can usually be found on microscopic examination, blood has only been seen by the naked eye after repeated and careful scrutiny.

Case 1. At the age of 36 years N. F. was treated for thyrotoxicosis with thiouracil. At that time she also complained of diarrhoea, with six to eight motions daily. Diarrhoea persisted without remission for seven years, after which she was admitted to hospital. She was passing up to eight motions in 24 hours, and also complained of a dull ache in the hypogastrium. The stools contained undigested meat-fibres, although no red cells or pus could be seen on

microscopy. Over 7 gm. of fat per day was excreted while the patient was taking a diet containing 50 gm. of fat. A blood count showed 4,180,000 red cells per c.mm., haemoglobin 10·8 gm. per 100 ml., and 4,600 white cells per. c.mm. The X-rays of this patient, showing the involvement of the ileum and ascending colon, have been published elsewhere (Brooke, 1954, Fig. 9).

More difficult are cases of ileocolitis which present few clinical features to distinguish them from ulcerative colitis, so that the enteritis is overlooked. In these patients the condition may take on a more intermittent character and, as the inflammation in the colon increases and spreads, the stools contain more obvious blood and pus. In an acute phase food is often visible in the motions, which in periods of relative quiescence return to normal consistency or to being bulky and pale. Abdominal pain, varying in intensity and situated around the umbilicus, is often complained of, and may be an indication of the ileitis. Sore tongue, ulcers in the mouth, and other evidence of vitamin deficiency are perhaps more common in this condition than in ulcerative colitis, while erythema nodosum has sometimes affected the skin. The clinical picture may be better illustrated by case histories; in three patients the illness has been severe and present for a long time.

Case 2. D. E., a housewife aged 39 years, began to have attacks of diarrhoea at the age of 30 years, with frequent fluid stools which were pale and offensive. The diarrhoea occurred each year during the months from March to October. Her skin tanned easily in the sunlight, especially the face, neck, and back of the arms, and on many occasions she also had a sore mouth, with ulcers on the tongue. During winter her stools became normal in colour and consistency, though occasionally containing blood from her piles. On her first admission to hospital, however, the stools were fluid and mixed with blood and mucus, occurring five or six times during 24 hours and principally at night. On examination she was 5 ft. 6 in. tall, and weighed 116 lb. Pigmentation was heavy on the extensor surfaces of the forearms, the face, and the neck; on the face and neck it faded in hospital, leaving patchy pigmentation. The tongue was smooth; the lips and inside of the mouth were normal, with no pigmentation. The heart, lungs, and central nervous system showed no abnormality. Sigmoidoscopy revealed granular proctitis and colitis, with haemorrhagic areas scattered over the mucous membranes and a small amount of exudate. A blood count showed red cells 2,730,000 per c.mm., haemoglobin 5·5 gm. per 100 ml., white cells 5,900 per c.mm., packed cell volume 23 per cent., mean corpuscular volume 84·2 c.μ, and mean corpuscular haemoglobin concentration 23·9 per cent. The blood film showed a mixture of normocytic and macrocytic hypochromic cells, with many target cells. There was delay in transit of barium through the small intestine, with distension of the terminal ileum at four and six hours (Brooke and Cooke, 1951, Fig. 1). A barium enema gave the appearances of ulcerative colitis, but the 'evacuation' films showed that barium persisted in the colon for three hours, at which time the haustration had almost returned to normal. Fat-balance tests over 72 hours revealed only 82 per cent. absorption on a diet containing 50 gm. of fat. The serum-albumin was 3·1 gm. and serum-globulin 2·1 gm. per 100 ml. On microscopic examination of the faeces occasional pus-cells and many red cells were to be seen.

Some improvement was obtained from rest in bed and blood transfusions, but after her discharge from hospital the diarrhoea recurred, the attacks lasting from one to two weeks, and when the patient was readmitted three years later

she was again having six to eight motions daily. The latest recrudescence of diarrhoea had been sudden, and the stools, which were offensive, contained much blood and mucus, while on four occasions she passed mucofibrinous casts up to 12 cm. in length. She had continuous fever, which reached 102° F., and an extensive rash of erythema nodosum on the thighs and legs, and her ankles were swollen. Although blood was frequently seen macroscopically, microscopy of the faeces on a number of occasions revealed only fatty-acid crystals. She was excreting 15 to 20 gm. of fat daily in her stools. A progress meal with weakly flocculating barium ('raybar') revealed considerable delay, dilatation of the upper intestine, and contracture of the lower six inches of the ileum together with poor motility and mucosal abnormality; a barium enema showed a lack of haustration in the colon and irregularity of contour (Plate 1, Fig. 4). Hyperaemia of the bowel wall and much mucus were seen on sigmoidoscopy, while there was evidence of scarring together with a few small ulcers, an appearance compatible with active proctitis and colitis.

Case 3. J. B., a man aged 42 years, came under observation with a diagnosis of ulcerative colitis for consideration of colectomy. He had been perfectly well until 10 years previously when, after pain in the left side of the abdomen, he developed severe diarrhoea, passing motions every hour. The diarrhoea ceased while he was treated with sulphasuccidine, but recurred on withdrawal of this drug. It then persisted and was associated with anaemia, and throughout his illness he had frequent sore throats and ulceration of the mouth, pharynx, and tongue, which at times were of such severity as to cause serious restriction of food. Initially his weight had been 13 stone, but after a loss of 3 stone it had become constant at 11 stone. According to his own statement his motions had been liquid since the onset of his illness, occasionally mixed with blood and mucus, and sometimes pale, sometimes normal in colour. His appetite was good.

On admission to hospital he was pale, with koilonychia, and a number of shallow ulcers on the palate and uvula; the liver was slightly enlarged, and the spleen was just palpable. Macroscopically the stools were loose, almost liquid in consistency, and contained mucus and sometimes blood; microscopically blood, pus, and fatty acids were present; there was no excess of meat-fibres. Sigmoidoscopic examination showed an inflamed rectal mucosa with a membrane of exudate; no discrete ulceration was seen. These appearances were compatible with ileal or colonic lesions. Laboratory investigations showed red blood-cells 3,980,000 per c.mm., haemoglobin 6·1 gm. per 100 ml., mean corpuscular volume 72·1 c.μ, mean corpuscular haemoglobin concentration 23 per cent., and white blood-cells 4,900 per c.mm. Fat-excretion on a 50-gm. fat intake showed a mean excretion of 10 gm. per day for four days. Liver-function tests showed serum-albumin 4·1 gm., serum-globulin 4·4 gm., total cholesterol 188 mg., and serum alkaline phosphatase 14·3 units per 100 ml. Examination two months later showed serum-albumin 3·8 gm., serum-globulin 3·3 gm., total cholesterol 290 mg., and serum alkaline phosphatase 48 units per 100 ml., with the thymol turbidity 4·0 units and the colloidal gold test (MacLagan) strongly positive. Further estimation of the serum alkaline phosphatase and flocculation tests during the next three months confirmed these abnormal features. Glucose-tolerance tests showed the fasting blood-sugar to be 90 mg. per 100 ml., rising to 125 mg. at the end of one hour and falling to normal levels in two hours. Duodenal intubation, with intravenous secretin administration, showed grossly inadequate volumes of pancreatic secretion and minimal quantities of amylase and bicarbonate. Moderate dilatation of the intestine, particularly marked in the terminal ileum, was revealed by a 'raybar' progress meal, and a rounded

calcified mass was shown either in the root of the mesentery or in the tail of the pancreas. On a barium enema normal haustration of the colon was seen, but irregularity of the mucosal surface was reported by the radiologist as indicative of ulcerative colitis (Plate 1, Fig. 5).

Subsequent progress is indicated in Fig. 1, in which the number of stools and quantity of water and fat are depicted. Little effect was produced with varied

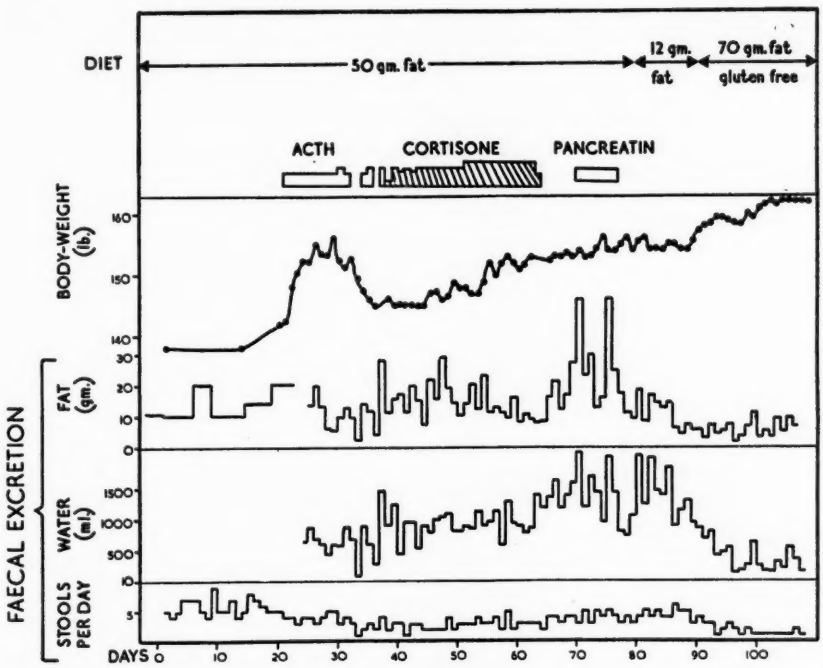

FIG. 1. Case 3. A man aged 42 years with ileocolitis. Changes in body-weight and faecal excretion.

treatments, which included corticoids, in spite of overdosage with both corticotrophin and cortisone. Owing to the patient's intolerance of a number of different oral preparations of iron, the anaemia could only be controlled satisfactorily with intravenous therapy. His oral and pharyngeal ulcers and dysphagia cleared rapidly after the administration of both folic acid and vitamin B_{12}; eventual improvement in the watery diarrhoea occurred after the administration of a gluten-free diet.

Case 4. Eighteen months before coming under our care, J. H. N., a man aged 37 years, noticed blood after defaecation on a number of occasions, especially after any strenuous activity. At that time he was passing two formed stools daily, of normal colour, and he denied the occurrence of diarrhoea at any time in the past. The appearance of blood in the stools persisted, and seven months later he experienced a sudden increase in the number of stools, up to 10 per day. Owing to the persistence of the diarrhoea he was sent to a hospital, where sigmoidoscopy and barium-enema examination were carried out, and a diagnosis of ulcerative colitis was made. After two further admissions to hospital on

account of exacerbations of diarrhoea, he was referred to us with a view to colectomy. During all this period he had lost only a few pounds in weight, had had no glossitis, and had complained of some lower abdominal pain prior to defaecation.

On admission to hospital he appeared well nourished, with no evidence of anaemia or glossitis; some tenderness was present in the abdomen along the line

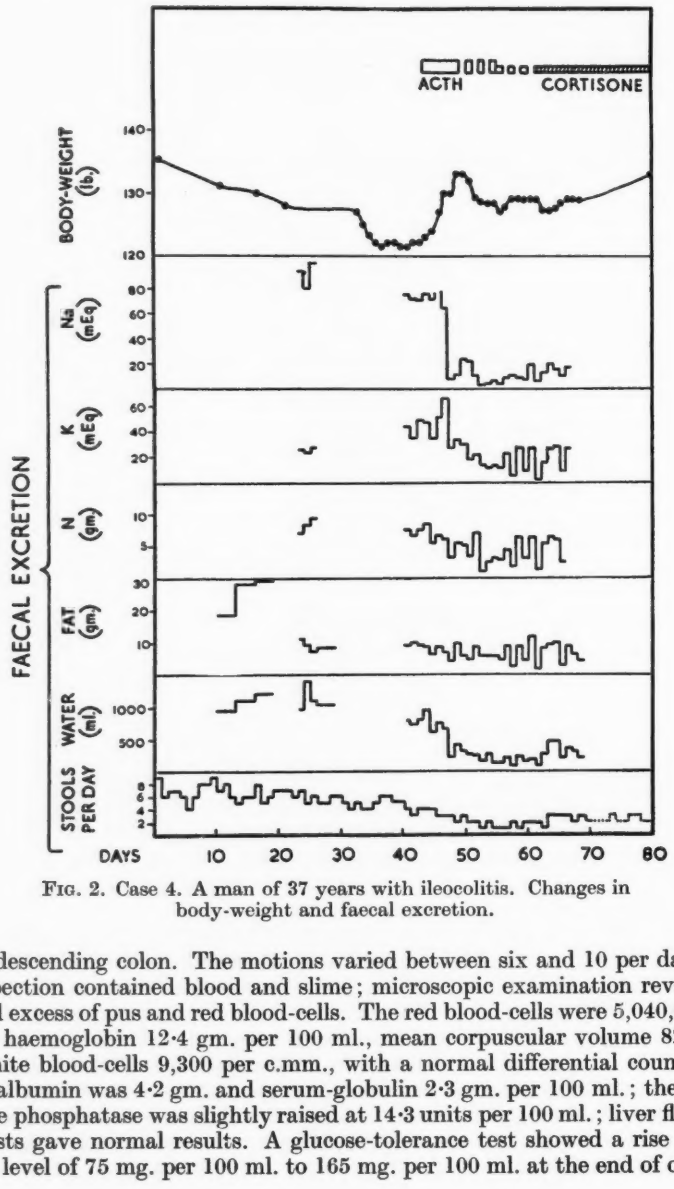

FIG. 2. Case 4. A man of 37 years with ileocolitis. Changes in body-weight and faecal excretion.

of the descending colon. The motions varied between six and 10 per day, and on inspection contained blood and slime; microscopic examination revealed a marked excess of pus and red blood-cells. The red blood-cells were 5,040,000 per c.mm., haemoglobin 12·4 gm. per 100 ml., mean corpuscular volume 82·1 c.μ, and white blood-cells 9,300 per c.mm., with a normal differential count. The serum-albumin was 4·2 gm. and serum-globulin 2·3 gm. per 100 ml.; the serum alkaline phosphatase was slightly raised at 14·3 units per 100 ml.; liver flocculation tests gave normal results. A glucose-tolerance test showed a rise from a fasting level of 75 mg. per 100 ml. to 165 mg. per 100 ml. at the end of one and

a half hours, falling to fasting levels at two and a half hours. The report on sigmoidoscopy was: 'No anal lesions seen. The lower rectum is only mildly inflamed, and in a somewhat patchy manner, rather resembling fungoidal infections of the skin. In the upper ampulla the inflammation increases. The tone of the bowel wall is also increased, so that it was impossible to circumnavigate the rectosigmoid junction owing to spasm; blood and pus were mixed with fluid faecal material.' Radiological examination of the colon by a barium enema showed no abnormal features apart from a rectum of small capacity and slight irregularity in the sigmoid colon. A progress meal with 'raybar', however, showed dilatation of the jejunum, while the outstanding feature was the rapid transit of the meal, which reached the caecum in 15 minutes and the rectum in 90 minutes. The appearances of the ascending and transverse colon suggested mild colitis.

The patient's course in hospital, and the biochemical findings associated with the discovery of steatorrhoea, are shown in detail in Fig. 2. Treatment only with rest in bed produced no amelioration in the diarrhoea, the volume of faeces remaining about one litre per day. The administration of corticotrophin (ACTH, Armour) intravenously resulted in a rapid improvement in the stools, which after five days' administration became solid for the first time in six months. Change to oral cortisone resulted in some increase in the number of stools, while the patient still maintained good control. He was discharged from hospital on a maintenance dosage of cortisone 25 mg. daily.

Other patients may come under observation at an earlier stage, but with a less severe attack; one such patient (Case 5) has been briefly reported elsewhere (Cooke, 1952) and suffers from recurrent attacks of diarrhoea, the stools often being pale and containing excess of fat, blood, and mucus. The sigmoid and rectum are normal in appearance on sigmoidoscopy, but X-ray examination of the ascending and transverse colon shows evidence of 'colitis'. She is, however, free from diarrhoea for long periods, and able to carry out strenuous academic and athletic activities. Some are not so fortunate, for occasionally an acute fulminating enterocolitis may be encountered which leads eventually to the patient's death (see also Case 9).

Case 6. Ten weeks prior to his admission C. W., a youth of 17 years, began to have diarrhoea, which gradually became worse, with five or six motions every day. Diarrhoea was more marked at night and in the early morning. He continued to pass considerable blood and flatus, and complained of central abdominal pain. He was then admitted to hospital, where he was found to be febrile and to have lost nearly 3 stone in weight. His haemoglobin was only 6·4 gm. per 100 ml. Sigmoidoscopy at this time revealed a 'very granular appearance of the whole of the rectal mucosa, with some oozing of blood, although this was coming mainly from beyond the recto-sigmoid junction. There was little ulceration, but the changes in the rectal mucosa were what might be expected in ulcerative colitis. No haemorrhoids were seen'. Microscopic examination of the faeces showed pus and blood-cells. He was given a blood transfusion, but his condition began to deteriorate, with pyrexia, severe dehydration, and pronounced faecal incontinence. At this stage he was transferred to our care.

On admission he was febrile, pale, and toxic, with marked dehydration and a distended, tender abdomen. His temperature was 103° F., pulse 120, and blood-pressure 110/70. The faeces contained no blood and little mucus; they

were occasionally pale; fluid loss was difficult to control even with intravenous therapy. Biochemical examinations revealed the presence of excess of fat and nitrogen in the stools, suggesting the diagnosis of enterocolitis, which was supported by radiological examination (Plate 1, Fig. 6). ACTH therapy was begun by the intravenous route; 20 mg. daily had little effect, but the pyrexia abated with a dose of 30 mg. daily. At this time he developed a severe monilial infection, a legacy of previous chloromycetin therapy, which caused persistent

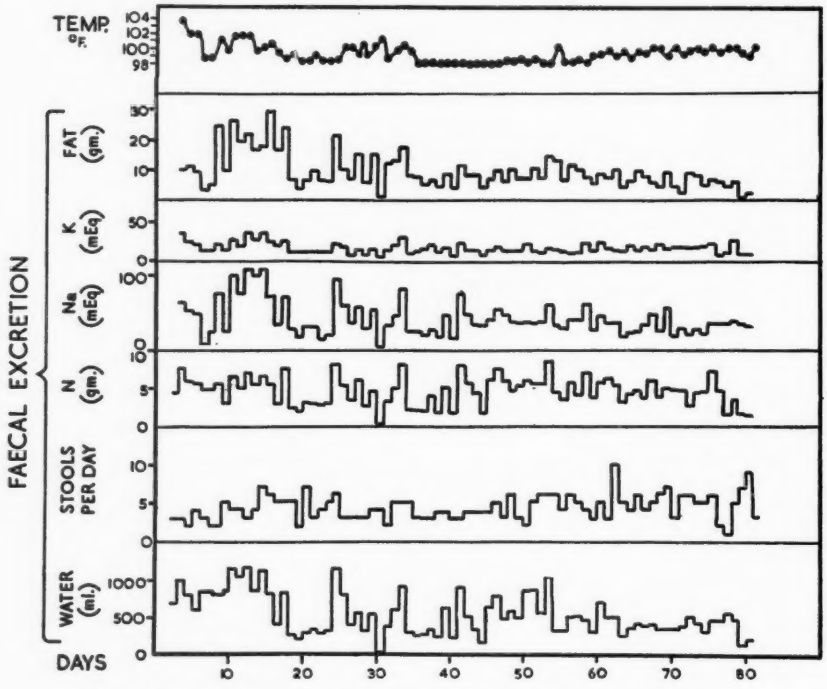

FIG. 3. Case 6. A youth of 17 years with ileocolitis. Temperature and changes in faecal excretion.

trouble, though it was eventually controlled by gentian violet. His improvement was further hindered by pyelonephritis, due to coliform and proteus organisms, and responding only to aureomycin. It will be seen that the steatorrhoea eventually subsided, though the nitrogen excretion remained high and the stools watery (Fig. 3); but he then began to vomit as a result of intestinal obstruction. At laparotomy the obstruction could be relieved only by separating a fistulous communication between adherent ileum and transverse colon, for the adherent loop of small bowel had snared another intestinal loop. Much of the small intestine below the obstruction was found to be thickened and hyperaemic; there were also numerous adhesions. After this operation the diarrhoea became worse, and it was soon evident that, while the small intestine had recovered almost completely, the colon was seriously damaged. Ileostomy was performed as a measure of last resort, and at this operation it was noted that the appearance of the small intestine had improved, whereas the colon remained grossly thickened and adherent to the abdominal wall. The patient's pyrexia and vomiting subsided, but two subsequent operations became necessary for the

relief of obstruction by bands; no further evidence of ileitis could be seen at either operation. After the final operation the patient died, and at autopsy no abnormality could be seen in the jejunum or ileum, while the mucosa of the colon was destroyed and its wall grossly thickened, fibrotic, and adherent.

Finally there are patients who develop severe and permanent changes in the colon, as well as the steatorrhoea syndrome with an associated macrocytic anaemia. One such patient (Case 7) has already been briefly commented upon by Snell (1949) and described by us elsewhere (Brooke and Cooke, 1951). She had considerable glossitis, and deep pigmentation of the face, neck, and extensor surfaces of the hands; gross steatorrhoea, hepatomegaly, and splenomegaly, and a persistent macrocytic anaemia were found. Radiological examination of the small intestine was reported as showing 'definite abnormality of the distal ileum, with irregular "moth-eaten" and dilated gut. The caecum is shrunken and fibrosed and high under the liver, the transverse colon being straight and pipe-like with filling defects due to pseudo-polyps'. (For X-rays see Brooke, 1954, Fig. 5.) For the last five years of her life she was completely incapacitated by her persistent diarrhoea. She died suddenly after a severe intestine haemorrhage. There was no autopsy.

Case 8. A. L., a schoolmaster aged 42 years, was admitted on account of diarrhoea, loss of weight, sore tongue, and swelling of the ankles. For as long as he could remember his bowels had opened three or four times daily; nine years prior to admission, during his first attack of diarrhoea, he noticed that his motions were light in colour and semi-solid. Diarrhoea, with up to 20 motions daily, became persistent during the two years preceding his admission, and during this time he noticed some blood, but no mucus, in the stools. Recently he had been troubled with vomiting. On examination he looked sallow and ill; his tongue was smooth, with some red patches. His temperature rose in the evenings to between 100° and 101° F., while tachycardia, initially 120, rose to 150. There was finger clubbing and marked oedema of the legs. The abdomen was distended; the stools were pale and fatty, and contained an excess of fatty-acid crystals, but neither blood nor pus-cells. He had a macrocytic anaemia; the red cells were 3,980,000 per c.mm., haemoglobin 11·1 gm. per 100 ml., and mean corpuscular volume 100·7 c.μ; the serum-albumin was 2·4 gm. and serum-globulin 2·6 gm. per 100 ml. At sigmoidoscopy the rectum was seen to be inflamed, while barium studies revealed multiple 'saw-tooth' areas in the small bowel and a diffuse colitis, with a stricture in the transverse colon and dilatation of the colon proximal to it (for X-rays see Brooke, 1954, Figs. 6 and 7).

In spite of his desperate condition, operation was undertaken in order to overcome the obstruction caused by the stricture in the transverse colon. At laparotomy the liver was found to be so grossly fatty that only a palliative resection could be considered for a stricture which was probably carcinomatous; histological section later proved this to be so. During operation the lower ileum was seen in parts to be reddened and thickened, but not greatly so. The patient died four days afterwards. At autopsy the extreme degree of fatty degeneration in the liver was confirmed; no leak had occurred at the anastomosis. The small intestine, from the lower jejunum onwards, was diffusely involved with shallow ulcers, about $\frac{1}{8}$ in. across, and intervening mucosal oedema, though towards the lower ileum the whole depth of the bowel wall was thickened and oedematous, as was the colon proximal to the obstruction

(Plate 2, Fig. 7); there was no obvious collagenous deposition, nor any cicatrization. The mucosa of the colon appeared to be almost completely destroyed throughout.

Radiology

The importance of careful radiological examination of the small intestine in the diagnosis of enterocolitis needs no emphasis. In our experience, however, the successful demonstration of abnormalities in both large and small intestine varies with the patient, and depends upon the skill of the radiologist. We have used both flocculating and weakly flocculating barium ('raybar') (Ardran, French, and Mucklow, 1950) in most instances for the examination of the small intestine. Both have their value in demonstrating either the flocculation caused by the excess of mucus in the lumen (Frazer, French, and Thompson, 1949) or the dilatation of the ileum. Deficiency patterns of the small intestine have been described as occurring in ulcerative colitis (Mackie and Pound, 1935; Mackie, Miller, and Rhoads, 1935; Posey and Bargen, 1950). In some, at least, of the patients recorded by Posey and Bargen steatorrhoea was present. From other evidence in their report it is possible that these examples were similar to the cases we are now reporting. At this clinic progress meals with flocculating barium have been carried out in many patients who had classical ulcerative colitis; in none of them was there evidence of a 'deficiency pattern'. In our opinion the finding of such a radiological abnormality is evidence of disordered function of the small intestine, though in the absence of further supporting evidence this disorder may be of a relatively temporary nature, such as that due to electrolyte depletion. Finkelstein (1950) has rightly stressed the difficulties of interpretation. 'It must be admitted, however, that the most common problem in differential diagnosis arises in the attempt to distinguish the early stages of non-specific enteritis and enterocolitis from minor phases of small intestinal motor dysfunctions or slight irritability in a colon not cleansed sufficiently to reveal its mucosal pattern. Even when the first examination has been done carefully, in such doubtful cases an even more careful and detailed re-examination is usually required before one can decide whether or not organic pathology is present.' Among the difficulties to be encountered is the contraction of the right side of the colon, so that the ileocaecal valve and caecum are difficult to identify. With the dilatation of the ileum this identification of the junction between ileum and colon becomes doubly difficult. In all our patients, therefore, particular attention has been paid to the condition of the terminal ileum and ascending colon. The radiological appearances in the colon differ but little from those seen in ulcerative colitis, since, as well as contraction in length and loss of haustration, pseudo-polyposis may be observed. One important difference is to be found in the anatomical site, for the colon in enterocolitis is abnormal on the right side in the early stages, whereas ulcerative colitis affects the descending and sigmoid colon most severely. When enterocolitis has persisted so long that the whole colon has become diseased, the differentiation from ulcerative colitis cannot be made from the radiological appearances of the large bowel alone. Extensive flocculation of barium and dilatation of the small

intestine were encountered in several patients; in all there was some abnormality to be detected in the terminal ileum, principally dilatation, and often an irregularity of mucosal outline, the normal blunt or round ends of each mucosal fold being sharpened to a point, giving a 'saw-tooth' appearance.

Pathology

External appearance of the bowel. The impression gained at laparotomy may be deceptive, for, unlike Crohn's cicatrizing lesion, the small bowel in enterocolitis does not develop collagenous thickening, nor does it commonly proceed to adhesion to other organs and fistula formation. The lesion is confined to the mucosa, so that its presence may not be revealed either on inspection or on palpation, though in advanced cases, such as Case 8, oedema may be detected, and even areas of hyperaemia may be visible. It is more common to see changes in the colon, the wall of which can appear opaque or actually reddened in an exacerbation, more particularly in the ascending colon (for example, Brooke and Cooke, 1951, Case 3).

Case 9. J. P., a woman of 24 years, was admitted to hospital on account of diarrhoea, which had started three months previously, with up to 15 motions daily. At the outset her temperature was 104° F. and pulse 120; her condition deteriorated, with an increase of abdominal pain, and laparotomy was performed on the diagnosis of perforation supervening on ulcerative colitis. No perforation was found, but the caecum and ascending colon were seen to be inflamed and thickened; a note was made that the ileum was unaffected. The diagnosis of acute enterocolitis was, however, made two days later, for on proctoscopic examination the changes in the rectum were considered to be too slight for ulcerative colitis. She died 10 days after operation, and at autopsy the small bowel was found to be involved in a diffuse enteritis: the jejunal mucosa was hyperaemic, and below this region shallow irregular ulceration persisted down to the ileocaecal valve. The ulceration present in the caecum and ascending colon diminished progressively in a distal direction. The liver was grossly fatty.

Internal appearances of the bowel. In the small intestine the lesion is confined essentially to the mucosa, and in the two autopsy specimens seen (Cases 8 and 9) consisted of multiple small ulcers, about $\frac{1}{8}$ in. in diameter, distributed throughout the distal three-quarters of the small intestine. The intact mucosa between these ulcers appears normal in the upper intestine, but becomes progressively more oedematous as the ileocaecal valve is approached. The whole depth of mucosa is lost at the site of ulceration. Histological examination only confirms the macroscopic appearances, and reveals no specific feature. The appearances differ markedly from those of ileitis secondary to ulcerative colitis; in the latter disease the 'back-wash' through the incompetent valve produces a uniformly granular appearance confined to the lower one or two feet of the intestine. They also differ from Crohn's cicatrizing lesion, with its considerable thickening affecting all layers of the wall, its tendency to adherence and fistula formation, and its localization to well-defined areas. In the colon the disease is at first confined to the right side, where the mucosal destruction does not resemble the ulceration in the ileum but differs in no way from that seen in ulcerative colitis except as

regards its site, since in ulcerative colitis destruction is greatest in the descending and sigmoid colon, while the caecum and part of the ascending colon are frequently spared. With the passage of time the whole large bowel is involved; it is then difficult to distinguish the colon of enterocolitis from that of ulcerative colitis. The gradual progression of the disease down the colon lends colour to

Liver-Function Tests and Fat-Excretion in Patients with Ileocolitis

Case number	*Sex*	*Age (years)*	*Serum-albumin (gm./100 ml.)*	*Serum-globulin (gm./100 ml.)*	*Serum alkaline phosphatase (units/100 ml.)*	*Serum-cholesterol (mg./100 ml.)*		*Flocculation and turbidity tests*			*Daily fat-excretion (gm.)*
						free	*ester*	*thymol (units)*	*cephalin-cholesterol*	*colloidal gold*	
1	F	43	4·5	3·3	16·9	82	150	2·0	Negative	532	7
2	F	39	3·7	1·4	4·5	35	45	0·5	Negative	221	20
3	M	42	4·1	4·4	14·3	84	104	0·5	Negative	210	10–20
4	M	37	4·2	2·3	14·3	73	104	3·0	Negative	443	10–20
5	F	20	3·7	2·2	3·8	70	140	0·5	+	221	7
6	M	17	3·8	2·0	6·3	47	60	0·5	+	321	5–25
7	F	40	3·2	4·7	38·2	92	134	5·0	++	554	25
8	M	42	2·4	2·6	11·3	38	48	3·0	+	433	..
10	M	19	3·2	2·4	32·9	75	101	6·0	++	112	8–40
11	F	10	1·64	1·4	21·6	..	..	4·0	..	..	8–9
12	M	33	3·7	1·9	5·5	22	118	1·0	Negative	221	4–20
13	M	39	3·1	2·3	..	..	..	..	..	..	8
14	M	30	4·6	1·7	7·7	87	125	3·0	++++	321	8
15	F	32	3·7	3·1	5·5	61	192	4·0	+	122	9
16	M	32	4·2	2·2	9·9	32	160	3·0	Negative	332	11

The figures under daily fat excretion were recorded while the patients were on a diet containing 50 gm. fat. Single figures indicate mean excretion over three days; a range of figures is shown where daily excretions were estimated for at least six days.

the suggestion that the colitis is a phenomenon secondary to the lesion in the small intestine and the discharges poured down from it.

Complications

Such features as anal fistulae and fissures, which are commonly associated with colitis, are to be seen in this condition. The remote complications of ulcerative colitis, such as arthritis and iritis, have not been manifest, but erythema nodosum has been seen. Carcinomatous change arising from long-standing disease in the colon is a hazard in enterocolitis, as in ulcerative colitis (Case 8). Though acute complications such as perforation and haemorrhage have not been encountered, peritonitis, due to an exacerbation producing an acute inflammatory change in the right colon, has occurred (Case 9).

The Liver

A feature that we have noticed in our group of patients has been the frequent finding of evidence of liver damage. Gross fatty change in the liver, even in what seemed to be a relatively early stage of the disorder, was also seen in patients who came to autopsy, and in the two patients submitted to laparotomy. In other patients there was clinical, and often laboratory, evidence of liver

damage (see Table), one patient at least having associated oesophageal varices. Splenomegaly was sometimes present.

Case 10. R. S., a man aged 19 years, had been well until the age of nine years, when he had an attack of diarrhoea during which he passed some bright blood; this attack only lasted a few days. The diarrhoea however recurred, so that for the next 10 years the stools were not less than six per day. He had many attacks lasting two or three weeks, during which bright red blood would be present in the motions, usually at intervals of about two to six months; only occasionally had mucus been noted in the stools. On no occasion during these 10 years had he passed a formed motion. Except for severe tenesmus during the attacks of bleeding, he had had no abdominal pain. He was retarded in development, being stunted and having poorly-developed secondary sexual characteristics, with scanty pubic and axillary hair; for he had ceased to grow since the onset of his diarrhoea. There was a mild degree of finger clubbing. Except for the findings of a grossly enlarged liver and spleen, physical examination was negative. Sigmoidoscopy revealed the rectal mucosa to be much thickened, and several small pseudo-polypi were seen in the lower rectum; the bowel wall was lined with a granular, oedematous, bleeding membrane, so thick that in most parts it was a creamy white colour. Microscopic examination of the stools showed pus-cells, occasional red blood-cells, and a marked excess of neutral fat, fatty-acid crystals, and undigested meat-fibres. The daily excretion of fat in the faeces varied between 8 gm. and 40 gm. during 12 days, the mean being 28 gm. A glucose-tolerance test gave normal results, but a chylomicrograph curve was flat; the 17-ketosteroid output per 24 hours was 3 mg.; duodenal intubation revealed small amounts of trypsin, amylase, and lipase. The red blood-cells were 4,170,000 per c.mm., haemoglobin 7·2 gm. per 100 ml., mean corpuscular volume 68·4 c.μ, and mean corpuscular haemoglobin concentration 24·3 per cent. A Congo-red test for amyloid was negative. Liver-function tests were abnormal (see Table). Radiological examination showed evidence of small-intestinal deficiency, and in the colon a grossly disorganized mucosal and muscle pattern. He was treated with blood transfusions and a high-protein, low-fat diet, with little effect. He died at home six months later. There was no autopsy.

Case 11. V. C., a girl of 10 years, developed frequent loose stools at the age of six years, and continued to have diarrhoea whenever she had an upper respiratory infection; after six months diarrhoea became continuous, with three to six yellowish motions per day occasionally streaked with blood. She was admitted to hospital, and was found to have a slightly enlarged liver; the spleen became palpable while she was in hospital. Sigmoidoscopy showed a reddened and oedematous mucosa, a finding compatible with colitis. The stools were pale, loose, offensive, and streaked with blood, and contained a few pus-cells on microscopic examination. There was no significant anaemia at this time. Until the age of 11 years, when she died, she continued to have frequent stools, occasionally as many as 12 per day, on some occasions only two. Meanwhile the liver and spleen grew larger; the liver-function tests became grossly abnormal, and in the last six months of life spider naevi developed on the face, in association with a marked caput medusae. A variable degree of iron-deficiency anaemia developed, which was rectified on many occasions by blood transfusion. Radiological examination of the small intestine indicated extensive involvement of the ileum, while the colon was shown to be a rigid structure lacking the normal haustration; the barium reproduced a granular appearance of the colon wall.

Daily fat-excretion, on a diet containing 50 gm. of fat, was 8 to 9 gm. A chylomicrograph curve was depressed; a glucose-tolerance test showed a rise to 280 mg. per 100 ml. at the end of one hour. She eventually died at home, with ascites and oedema of the ankles. There was no autopsy.

Much interest has been shown in the incidence of liver damage in ulcerative colitis since the reports of Tumen, Monaghan, and Jobb (1947), Pollard and Block (1948), and Ross and Swarts (1948). Even though much of the material reported was highly selected, it is evident that many patients with ulcerative colitis have liver damage, and many have developed hepatic cirrhosis (Kleckner, Stauffer, Bargen, and Dockerty, 1952; Kimmelstiel, Large, and Verner, 1952; Hoffbauer, McCartney, Dennis, and Karlson, 1953). It has been suggested that cirrhosis is more likely to develop when the onset of ulcerative colitis takes place during the early years of life (Jones, Baggenstoss, and Bargen, 1951). We have been surprised by the higher incidence of liver disorder in the present group of patients than in our far larger group of patients with ulcerative colitis, in whom liver-function tests have only occasionally been abnormal and cirrhosis of the liver has not yet been demonstrated, though fatty changes have not infrequently been encountered. Ross and Swarts (1948) regarded the hepatic insufficiency encountered in ulcerative colitis as being the outcome of loss of weight, anaemia, and marked extension of the disease.

Haematological and Other Findings

Nearly all the patients have had varying degrees of iron-deficiency anaemia at some time. Anaemia was severe in Cases 2 and 7, and in each of these patients varying degrees of macrocytosis have been present from time to time; both have needed blood transfusions. In Case 8 there was a moderate macrocytic anaemia. In the remainder the haematological findings were in no way specific, and the degree of anaemia was rarely severe. No examinations of the bone-marrow were made. Glucose-tolerance tests were carried out in 10 patients, but without significant results. Electrolyte balance varied with the degree of dehydration and nutrition.

Treatment

In the absence of knowledge of the aetiology, treatment has been empirical. Since all our patients have found that fried and meat fats tend to cause exacerbation of their intestinal symptoms, we have restricted the fat-intake. At the same time increased protein has been required, as for any recurrent or continuous diarrhoea, while in deference to tradition a diet low in indigestible roughage has been used. As for any chronic diarrhoea, rest in bed has proved beneficial, together with measures to replenish the electrolyte and water stores. Corticoid therapy has received commendation in the treatment of disorders both of the small intestine and of the colon (Elliott, Kiefer, and Hurxthal, 1951; Gray, Reifenstein, and Benson, 1951; Machella and Hollan, 1951). It was used with good effect in Case 4, and the patient's improvement was maintained with a small maintenance dose. The immediate effects are shown in Fig. 2, with the production of formed stools for the first time in six months. ACTH also induced

an improvement in Case 6, but only when given over eight hours in an intravenous drip; no permanent results could be produced owing to difficulties in this technique, and oral cortisone made no difference either to the course of the disorder or in ameliorating his diarrhoea. Neither cortisone nor ACTH had any significant effect on Case 3 (Fig. 1); in fact no improvement was obtained until the patient was put on a gluten-free diet, when the result was dramatic, and within a few days the stools had fallen from five a day to one or two a day, with a total water-content of less than 300 ml. per day, while the improvement in fat-absorption was only slightly less striking. It is too early to say whether the long-term results will be satisfactory, or what may be the exact significance of this observation.

Indications for surgery. There are not the clear indications for surgery in this condition that there are in regional ileitis and colitis, and in ulcerative colitis. The provision of an ileostomy may prove disastrous, for the small-bowel lesion is not circumvented thereby, and one patient previously reported (Brooke and Cooke, 1951, Case 3) died after this operation. Even should a serious catastrophe be avoided, there are great difficulties in controlling the faecal discharges from an ileostomy in patients with a disorder of small-intestinal function. A patient upon whom a colostomy had been performed for an epithelioma of the rectum became a complete invalid, owing to the difficulty of controlling the faeces during exacerbations of an associated idiopathic steatorrhoea. Even during periods of relative quiescence his stools were too voluminous to be contained adequately in the normal-sized ileostomy bag. In another patient, referred to us for consideration of ileostomy, ileosigmoidostomy and excision of the colon had previously been carried out for presumed ulcerative colitis. Examination of the colon after its removal had revealed it to be normal both macroscopically and microscopically. We found that the patient was suffering from idiopathic steatorrhoea; it proved difficult, however, to keep the bowel actions in check with such a short segment of large bowel remaining, and he suffered many episodes of acute electrolyte and water depletion. Alvarez (1949), in an editorial review of the involvement of the small intestine in the 'mucous colitis' syndrome, described a case which may well have been similar to those we have described. 'For many years before the coming of ulcerative colitis, the man had suffered from episodes which came every few weeks or months and lasted 24 to 28 hours. First he would suffer with malaise, lassitude, mild headache, and a feeling of intoxication, and then would come a feeling of abdominal fullness with distension, cramps, and perhaps rumbling and gurgling. All these symptoms were felt in the lower half of the abdomen. The usual diagnosis of an irritable colon was made. The interesting point was that after the ileostomy the patient continued to have the beginnings of his old attacks, but not the end symptoms. What happened was that after the malaise and the feeling of intoxication the ileal discharges became much more voluminous, and they kept pouring out of the stoma so frequently that the man was kept very busy changing the ileostomy bag. At the same time the discharge became more than usually irritating.' Butler (1953) has also recognized the dangers of ileostomy in these

patients. In addition he has resected wide areas, but the difficulty lies in recognizing the limits of the lesion in the small intestine, since it is not easy at operation to assess at what level normality ceases and abnormality begins. Furthermore, ulceration is extensive, so that ablative treatment, to be effective, calls for removal of such wide areas as to be almost prohibitive.

Vagal section has been reported as a method of treatment for 'ulcerative colitis' (Dennis, Eddy, Frykman, McCarthy, and Westover, 1948; Thorek, 1951; Eddy, 1951) and, as we have argued elsewhere (Brooke and Cooke, 1951; Brooke, 1954), it seems that this operation, when effective, may have been so in cases of small-intestinal disorder, and that some of these cases were in reality examples of enterocolitis; some, indeed, were diagnosed as Crohn's lesions. Though we have not tried this method of treatment, in one patient (Case 1) the stools became formed and reduced to one or two daily on the administration of banthine, and relapsed immediately on its cessation. In another patient (Case 12) banthine had no effect upon the frequency or consistency of the stools, which were passed 10 to 12 times daily. In view of the difficulty of controlling their frequency, and of the apparent progress of the colonic lesion, laparotomy was eventually undertaken, in the hope that ileosigmoidostomy could be performed and a potentially dangerous colon removed. At operation the small intestine appeared essentially normal, with no undue hyperaemia and no detectable thickenings; the colon, though somewhat opaque, was not unduly thickened, but the lymphatic glands draining the colon, and some of those in the mesentery, were enlarged. It was also noticed that colonic movements were readily stimulated by palpation. These findings in no way excluded the presence of mucosal lesions, which had indeed been demonstrated radiologically; nevertheless, it was decided not to resect the colon, since it appeared that the colonic damage had not advanced so far as to preclude the possibility of a remission. Ileostomy was contra-indicated by the clinical evidence of small-intestine disorder. Experience of a previous case had indicated to us that the intestines of such patients can sometimes heal (Case 13, Plate 3, Fig. 8).

To sum up, it is the continued diarrhoea and recurrent anaemia, both liable to be intractable to medical therapy, that cause surgery to be considered; but ileostomy is contra-indicated, and both resection of the ileum, together with the colon if necessary, and vagal section have yet to prove their worth.

Prognosis

Seven of our patients have died, and in one, who is not yet 45 years old, the colon is severely damaged. The acute form (Case 9) may prove rapidly fatal, and in cases of long standing, such as Case 8, the existence of secondary colitis over a long period introduces the hazard of carcinoma, as in ulcerative colitis. It is impossible, therefore, to regard this condition with equanimity. On the other hand many patients are leading an active life, their symptoms apparently being in complete remission. In Plate 3, Fig. 8 are shown the X-ray appearances of Case 13 over the last five years. This patient still gets an occasional

attack of diarrhoea, with loose, pale stools. His general health is good, and provided he avoids fried foods he is able to lead an active working life. A man aged 30 years (Case 14) has now lived seven years with similar findings, though in his case the radiological appearances of the colon have not improved. Another patient (Case 5) maintains satisfactory health. The natural history of this condition is as yet unknown, for no prolonged follow-up studies are available; it is therefore difficult to assess the prognosis fully. At present the lack of a specific medical or surgical remedy makes the prognosis poor in acute cases and cases without remission.

Discussion

Our thesis is based on the view that there is a group of conditions in which the small intestine is abnormal and the colon becomes involved secondarily. Hence the presence of excessive fat in the stools, reinforced by a deficiency pattern of the small intestine, is strong evidence in favour of an enteritis, while the development of blood and mucus in the motions, together with radiological evidence of 'right-sided' colitis, indicates damage to the colon. Nevertheless certain conditions may combine to give rise to a similar state of affairs. The incidence of pancreatitis in ulcerative colitis has been found as high as 53 per cent. in a series of 86 autopsies (Ball, Baggenstoss, and Bargen, 1950), and by Nabatoff, in another series of 45 post-mortem examinations, 33 per cent. (Dreiling and Richman, 1951). It cannot be said, however, that all the patients who had pancreatitis would have had steatorrhoea. Dreiling (1953) found that only 22 per cent. of his patients with chronic pancreatitis had steatorrhoea. It is clear that difficulties in clinical practice can arise. For example A. G., a woman aged 34 years, was investigated because of attacks of abdominal pain and diarrhoea, with the passage of blood and mucus, and was found to have ulcerative colitis. Pancreatic intubation showed complete absence of enzymes, and estimation of the faecal fat revealed an excessive daily excretion. At laparotomy for the performance of ileostomy the pancreas was found to be considerably thickened and reddened. At further laparotomy six months later for removal of the colon, the pancreas was reported as normal, while the condition of the colon was typical of ulcerative colitis. Steatorrhoea had then disappeared, and the pancreatic enzymes were present in normal concentrations. The difficulty was also evident in Case 3, in which the abnormal diminution of pancreatic enzymes justified the diagnosis of chronic pancreatitis; though this might well have been the primary aetiological factor in this patient, the therapeutic response to a gluten-free diet and the exacerbation of symptoms with pancreatic extracts suggest that the pancreatitis was secondary to the chronic intestinal disorder. Little has been published concerning the fat-excretion in ulcerative colitis; Posey and Bargen (1950) have noted steatorrhoea, but the clinical details they gave are not such as to allow comparison with our patients. They concluded that a variety of factors evidently combine to produce steatorrhoea: increased faecal solids, increased caloric loss in the stools, and deficiency states.

Crohn (1949) put the incidence of ileitis associated with ulcerative colitis at 24 per cent., but he included all cases of 'right-sided' colitis. The ileum becomes involved in ulcerative colitis when ulceration in the caecum has persisted so long as to cause the ileocaecal valve to become incompetent (Brooke, 1953, 1954). In such cases of secondary ileitis, however, insufficient small bowel is affected to induce a frank disturbance of function or evidence of failure of fat-absorption. In none of our patients in whom ulcerative colitis was proved by operation to be associated with secondary ileitis, however severe, has there been a defect of fat-absorption. Twenty-six of our group of over 100 patients with ulcerative colitis have been investigated for fat-excretion. In 25 the mean figure was 3·4 gm. $\pm$ 0·9 gm. per day, while in only one was there evidence of a fat-absorption defect. This patient, a woman, persistently excreted between 5 gm. and 9 gm. of fat when taking 50 gm. a day, though a progress meal showed no defect of small-bowel function, and at operation there was no evidence of a secondary ileitis; the possibility of pancreatitis was not considered, and therefore not investigated. After ileostomy and colectomy she did well, her weight increased from 91 lb. to 143 lb., and no further abnormality in fat-excretion was discovered. The initial fat-absorption defect in this one patient is therefore difficult to account for. Theoretically there should be no abnormal excretion of fat in ulcerative colitis, unless there is some other general systemic upset. Nevertheless certain complications which may take place during the course of ulcerative colitis can lead to extensive small-intestinal involvement. In rare instances amyloid disease complicates chronic ulcerative colitis; such patients have been reported by Olsan and Sussman (1948) and Jensen, Bargen, and Baggenstoss (1950). In these patients there was extensive involvement of the small intestine with amyloid, though no note was made of the occurrence of steatorrhoea, which has been reported by other observers (Adlersberg and Schein, 1947). The only patient with amyloid disease complicating chronic ulcerative colitis of whom we have had experience was passing pale stools at the time of his admission to hospital, but died after 48 hours, before any chemical analysis of the faeces could be made.

Pseudo-membranous enteritis has been reported by Penner and Druckerman (1948) as complicating ulcerative colitis. The aetiology of this condition is as yet unknown; in certain circumstances of dehydration and low blood-pressure vascular adjustments may take place which lead to ischaemia of the mucosa of the small intestine and, in fatal cases, to complete necrosis. A similar type of lesion can be caused by radiation injury (Amory and Brick, 1951). In either event, if the condition is not rapidly fatal, a severe enteritis will ensue, so that there will be steatorrhoea in addition to pus and blood in the stools. In one of our patients the process in the small bowel, resulting from deep X-ray therapy, gradually healed during three months, leaving the small intestine apparently normal by radiological and functional tests, though persistence of the colitis was proved by X-rays (Brooke, 1954, Fig. 47, Case 11). As yet there is no evidence that such acute lesions give rise to permanent disorder of intestinal function, though on theoretical grounds it would appear likely. We

have no evidence that the symptoms of any of our patients had followed the administration of antibiotics, a possibility that must be seriously considered in view of the observations of Reiner, Schlesinger, and Miller (1952).

Consideration must also be given to those patients whose symptoms and signs point predominantly to a diagnosis of idiopathic steatorrhoea. Sigmoidoscopy in such patients shows little abnormality unless the stools are frequent and diarrhoea is present. In such instances the sigmoid and rectum are hyperaemic and bleed easily, ulceration is not usually seen, and occasionally the pale stools may be mistaken for pus descending into the sigmoid from a higher part of the intestine. It was therefore of interest, in a patient suffering from idiopathic steatorrhoea who had a colostomy, to note the reactions of the colonic mucosa. With exacerbations of diarrhoea the mucosa became hyperaemic, and frequently bled when touched by the dressings; when the stools were well controlled it appeared quite healthy. The radiological appearances in certain patients with idiopathic steatorrhoea may also cause some confusion by simulating early ulcerative colitis. How do such patients differ from those described in the present paper? By the use of the term 'idiopathic' diagnosis by exclusion is implied, and the majority of patients with idiopathic steatorrhoea have no symptoms or radiological signs of 'colitis'; in a minority the 'colitis' syndrome is clearly subordinate to the disturbances due to idiopathic steatorrhoea. In a few cases differentiation may not be possible, as in Cases 2 and 7, for either of these patients might have started with such a functional disturbance of the intestinal tract. Since only the minority of patients with steatorrhoea have pale stools continuously, it is not surprising that occasionally the colon has been removed, under the erroneous impression that the severe watery diarrhoea was primarily colonic in origin. In one of our patients already alluded to this had indeed happened, and an ileosigmoidostomy had been performed; since the primary disorder was in the small intestine, he continued to have incapacitating attacks of diarrhoea. Steatorrhoea has been reported as being secondary to hepatic disorders (Gross, Comfort, Wollaeger, and Power, 1950), but it seems unlikely that our findings can be explained by a primary ulcerative colitis, which had caused hepatic disorder and so steatorrhoea. Both the published figures and our own experience show that cirrhosis of the liver, in the absence of any obstructive lesion, may not cause steatorrhoea.

Finally the relationship of the condition we have described to regional ileitis must be briefly considered. In no patient was there any evidence of a stenotic lesion of the small intestine. It is possible that the pathological changes described might progress to thickening, with the oedema and collagenous deposition associated with Crohn's lesions, but this process has not yet been observed, except perhaps in the colon in Case 6. The condition of non-stenotic ileojejunitis, as described by Marshak, Friedman, Wolf, and Crohn (1951), has some points of resemblance. In an account of their clinical findings there was an association of erythema nodosum, fever, and diarrhoea. There was also abdominal pain, diffuse in character, which they differentiated from that associated with obstruction. They commented that the diarrhoea, with the

presence of much mucus and little blood, might without careful study of the small intestine suggest ulcerative colitis. The condition in the majority of their patients seems to be more closely related to frank regional ileitis, but they referred to six patients in whom the X-ray findings were interpreted as showing early ileojejunitis; three of the latter patients were explored by an experienced surgeon, and no evidence of inflammatory disease was discovered. Further radiological studies of the small bowel, not unlike those we have seen, were reproduced by Mackie and Pound (1935).

The patients whom we have reported do not appear to have been suffering from any of the conditions discussed above, and should be considered as a separate group, with a disease simulating but different from ulcerative colitis and regional ileitis. With our lack of knowledge as to the causation of any of these disorders, it would be wrong to speculate further as to the aetiological differences between these conditions and enterocolitis, but the latter concept, by separating a clinical entity, may serve a useful purpose in clarifying lines of research. Patients will still be encountered suffering from chronic non-specific diarrhoea in whom a diagnosis of ulcerative colitis, regional ileitis, or enterocolitis is alike inadequate.

We wish to thank Professor W. M. Arnott, Dr. E. Bulmer, Professor T. L. Hardy, Dr. R. St. Johnston, and Professor J. M. Smellie, for permission to refer to their patients, and Dr. Garfield Thomas for the biochemical studies. We are indebted to the late Dr. A. L. Peeney for the haematological investigations. Fig. 7 *a* is reproduced by kind permission of Messrs. E. and S. Livingstone, Ltd.

Summary

1. A disorder is described which affects the small bowel primarily and spreads to the colon. It is different in its clinical, radiological, and pathological manifestations, and in its prognostic significance, from ulcerative colitis and from cicatrizing regional enteritis or colitis.

2. As in ulcerative colitis, and often in regional enteritis, diarrhoea is the predominant symptom. The disease may sometimes be suspected from the nature of the diarrhoea; cases are described.

3. The condition is characterized on the one hand by a disorder of small-bowel function, as shown by increased fat-excretion and radiological changes, and on the other hand by involvement of the colon, revealed by sigmoidoscopy and by X-ray evidence of abnormality in the ascending colon, later extending throughout the whole bowel.

4. Differentiation from other disorders associated with diarrhoea is discussed.

5. No specific treatment has been discovered; surgery should be avoided. Ileostomy, undertaken on the precept that the condition is a form of ulcerative colitis, has proved not only ineffective but dangerous.

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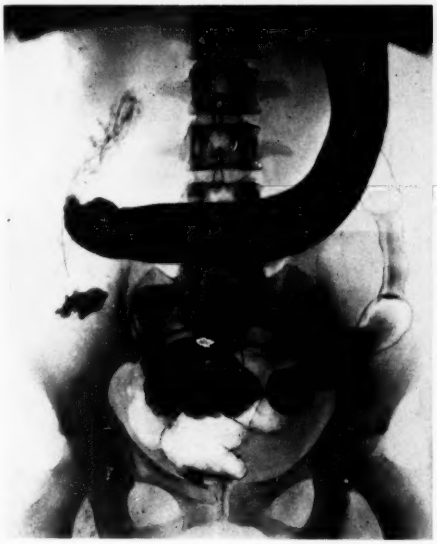

FIG. 4. Case 2. Barium enema, showing evidence of 'colitis'

FIG. 5. Case 3. Barium enema. Appearances resembling ulcerative colitis in the presence of steatorrhoea

(*a*) (*b*)

FIG. 6. Case 6. 'Raybar' progress meal to show (*a*) the jejuno-ileal disorganization and (*b*) the colonic involvement

FIG. 7*a*. Ileum in enterocolitis (Case 8)

FIG. 7*b*. Incompetent ileocaecal valve in ulcerative colitis, showing secondary ileal changes

(*a*)
February 1949. Progress meal

(*b*)
February 1949. Progress meal to show the ileocaecal region

(*c*)
January 1951. Barium enema

(*d*)
March 1953. Barium enema

FIG. 8. Case 13. X-rays to show stages of improvement

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COELIAC DISEASE: IS THERE A NATURAL RECOVERY?[1]

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The original observations of Dicke (1950) that children with coeliac disease improved when wheat flour and rye flour were excluded from their diets, and of Weijers and van de Kamer (1950) that there was an associated decrease in faecal fat, were confirmed in this country, in respect of wheat flour, by Anderson, Frazer, French, Gerrard, Sammons, and Smellie (1952), and later by Sheldon and Lawson (1952). It has also been shown that the harmful substance in wheat flour is present in the gluten fraction, and that when this fraction is excluded from the diet rapid improvement ensues (Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952; van de Kamer, Weijers, and Dicke, 1953). Although children frequently showed clinical improvement on earlier dietary régimes containing varying amounts of wheat gluten, this improvement was slow, and relapses were frequent. In fact some children who had coeliac disease retained both their symptoms and their steatorrhoea well into adult life (Bennett, Hunter, and Vaughan, 1932); conversely, many adults with idiopathic steatorrhoea have been shown to have a history of coeliac disease, diagnosed or presumptive, in childhood (Cooke, Peeney, and Hawkins, 1953). These facts prompted us to inquire whether children with proved coeliac disease, brought up on diets containing wheat, ever really recovered. We therefore decided to re-examine the children who had been diagnosed as suffering from coeliac disease in the Children's Hospital, Birmingham, before 1949, and who had not received treatment with a gluten-free diet, in order to assess their present state of clinical and biochemical recovery.

Patients and Methods of Investigation

The series comprised 32 children and adolescents whom we were able to trace; there were 20 female and 12 male patients, showing the usual female preponderance associated with coeliac disease. Their ages ranged from four to 19 years (for age distribution, see Table II). At the time of reassessment all were receiving normal diets, or diets restricted only in their fat content, and no patient was under active hospital supervision. When the original diagnosis of coeliac disease had been made the methods in use differed from those employed today. Exact comparison could not therefore be made of the condition of each child then and now, but an overall picture of the severity of the initial illness may be obtained from a brief summary of the main clinical findings.

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Initial clinical findings. In 22 children the first symptoms developed between the ages of eight months and 24 months, that is soon after the introduction of mixed feeding. In this group the classical coeliac triad of diarrhoea, abdominal distension, and loss of weight was observed in all the children except one. In the remaining 10 children the first symptoms did not develop until after the age of 24 months, and in five not until the age of four or five years. In this group the symptoms were failure to gain weight or actual loss of weight, and in some cases pallor or abdominal pain, or both, with vomiting; in only three cases was a history of loose stools obtained. All 32 children had some degree of iron-deficiency anaemia, and in 29 cases the haemoglobin was less than 11·3 gm. per 100 ml. Steatorrhoea, at that time defined as the excretion of more than 4 gm. of fat per day when the intake of fat was unknown, or a fat-absorption of less than 90 per cent. on a known intake of fat, was found in 29 of the children. It must be noted that the three who showed a normal excretion of dietary fat were assessed at a time when they were too ill to tolerate an intake of fat adequate for fat-balance studies. Their clinical history, however, was of classical coeliac disease, and they all had steatorrhoea at the time of their reassessment. In only 11 cases was it considered necessary to exclude fibrocystic disease of the pancreas by duodenal intubation and the demonstration of pancreatic enzymes.

Reassessment. When each subject was reviewed a careful history was taken, which included details of the diet and any persisting symptoms. Apart from a full physical examination a number of investigations were carried out:

Development. Weight and height were measured, and the percentage of the normal weight and height for age was calculated. Skeletal age was estimated by radiography of the centres of ossification in 22 subjects. The five adolescents in the series were examined for evidence of puberal development.

Intestinal function. 1. *Output of fat in the faeces.* This was measured by a modification of the daily-fatty-acid method described by van de Kamer, Bokkel Huinink, and Weijers (1949). In only 11 children was it possible to carry out fat-balance studies in hospital on a known dietary intake of fat. The remaining 21 patients, who were not admitted to hospital, were asked to bring a complete five-day stool collection for fat-analysis. One boy (Case 10), who was working, failed to comply. As some of these children were receiving diets restricted in fats, they were asked to take at least one pint of milk on the day preceding the test and daily for its duration. To serve as controls, a five-day faecal output of fat was investigated in each of a series of 20 children in hospital who were convalescent from parenteral disorders, and from the five-day figures the average daily output of fat by each child was obtained. These 'normal' control subjects were receiving an ordinary ward diet containing approximately 40 to 60 gm. of fat, that is, roughly the same fat-content as they would have received at home. The mean age of the control subjects was eight years, and that of the coeliac subjects 11 years. 2. *Absorption in the upper small intestine.* Oral glucose-tolerance tests were employed, and the blood-sugar was estimated over a two-hour period by the method of Hagedorn–Jenson. The dose of glucose was 40 to 50 gm., depending on body-weight. 3. *Radiography of the small intes-*

tine. The small-intestine pattern was examined after a barium meal and follow-through in 30 children, first with a flocculating and then with a non-flocculating preparation of barium sulphate. Particular attention was paid to flocculation of the simple suspension, and to the appearance of dilatation of the small intestine with the non-flocculating preparation.

Haematology. Red blood-cells, haemoglobin, packed cell volume, mean corpuscular volume, and mean corpuscular haemoglobin concentration were estimated in all 32 children.

Results

Clinical findings. No child was completely free from symptoms, although one mother considered that the original disorder had spent itself. The most frequent symptom was diarrhoea; it was constant in five cases and intermittent in 14. In three patients it was aggravated by colds, a feature frequently observed in acute coeliac disease. Abdominal colic was also common, and occurred in 15 children. Lassitude was present in 14; these children lacked the vitality of their siblings, and tired easily; one child of eight years, for example, was only able to go to school in the mornings. Only six patients had their original anorexia. Finger clubbing was detected in two children. Two children had suffered from rickets, and in one of them, a girl of 15 years who was considerably dwarfed, the disease was still active, as confirmed by X-rays and serum biochemistry (calcium 8·9 mg. per 100 ml., phosphorus 3 mg. per 100 ml., and alkaline phosphatase 140 King-Armstrong units). Two had had tetany, but none had tetany when reviewed.

Assessment of development. 1. *Height and weight*. Heights and weights were compared with normal standards; those of Engelbach (1932) as adapted by Wilkins (1950) were used, because they are based on a very large number of children of an adequate range of age. These standards are based on measurements taken over 20 years ago, but they are nevertheless in very close agreement, as Wolff (1954) has shown, with Daley's (1950) figures given for London school-children in 1949; in no case do the differences between the average heights for any given age exceed 0·3 in. *Weight*. Of the 32 children, 19 were 10 per cent. below the average weight for age, and one of these was 40 per cent. below the average weight for age. The mean reduction below the average weight for age was 12·4 per cent.; this is a highly significant reduction ($P < 0{\cdot}001$). *Height*. Nine children were 10 per cent. or more, and the two most stunted children 20 per cent., below the average height for age. The mean reduction below the average height for age was 7 per cent.; this again is a highly significant reduction ($P < 0{\cdot}00001$). This reduction in height of children who have had coeliac disease is shown diagrammatically in Fig. 1. In this figure the distribution about average height of the 30 children who had had coeliac disease, and who were five to 16 years old, is compared with the normal distribution about average height of the London school-children measured by Daley in 1949. In normal subjects variations in height are not so great as variations in weight, and it is for this reason that the reduction in height, though apparently less than the

reduction in weight, is the more significant. A further comparison between the average and actual weights for height revealed that the children were on average 5·5 per cent. above the average weight for height; this increase in weight above the average for height is just significant ($P < 0{\cdot}01$), and suggests that undernutrition due to malabsorption, though obviously contributing, was

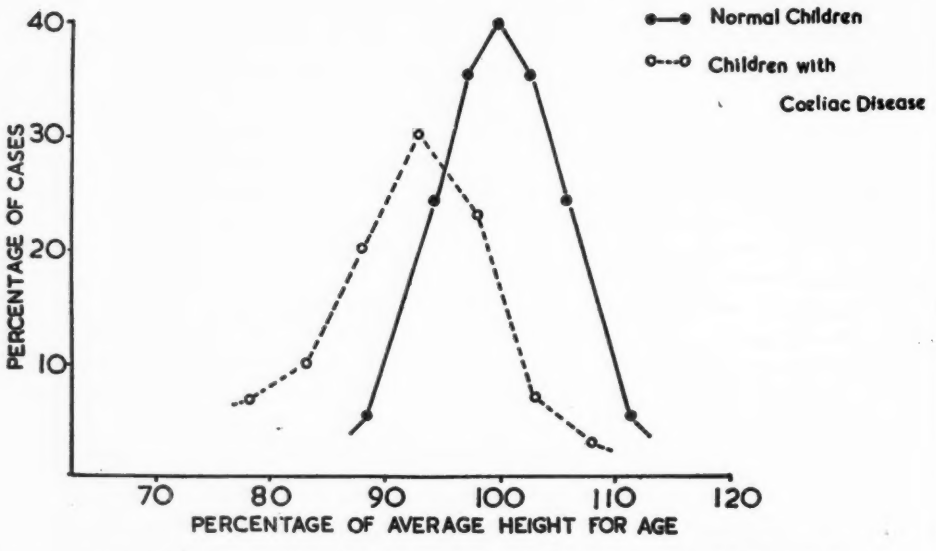

FIG. 1. The distribution about average height for age of normal children, aged five to 16 years (London County Council; Daley, 1950), compared with 30 children of the same range of age with coeliac disease. The maximum standard deviation for either sex has been taken in calculating the range of height in order to bias the results against the group with coeliac disease.

not the only factor responsible for the diminished stature of these children. Impaired absorption of specific growth factors probably also played a part.

2. *Skeletal age.* Radiographs of the centres of ossification were taken in 22 cases (Table I), and from these radiographs the skeletal age was calculated by using the tables of Vogt and Vickers (1938). Ossification was normal in 14 patients, of whom 12 were girls and only three were appreciably dwarfed; of these three one was a little taller than her mother, and was probably constitutionally small; another had severe rickets, which was the main cause of her stunted stature. Ossification was retarded in eight patients, of whom seven were boys; only one was of the average height for his age; the remainder were dwarfed, with a skeletal age that tended to approximate the calculated age for height. In the 14 patients whose skeletal age was normal the mean weight and height were only 5 per cent. below average; in the eight whose skeletal age was retarded the mean weight and height were respectively 21 per cent. and 11 per cent. below average. This difference indicates that skeletal age tends to be most retarded in the children who are most dwarfed; owing, however, to the

delay in ossification, such children will tend to continue to grow in height for a longer time, and it may be for this reason that the adult coeliac patient is not as stunted as might have been expected from his height in childhood.

3. *Puberty.* Of the five adolescents aged 15 years or over when re-examined, three were girls and two were boys. In two of the girls, aged 15 and 16 years, there was no breast development, and menstruation had not commenced. The other girl, aged 19 years, was fully developed, with regular menses which had started when she was 15 years old—two and four years later than in her two sisters. Both the boys were aged 16 years. Their voices had not yet broken, nor did they require to shave. It was of interest that one of the boys had a non-identical twin brother who had been shaving for two years, and whose voice had broken 12 months previously.

TABLE I

A Comparison of Chronological Age, Skeletal Age, and Apparent Age for Height

	Chronological age (years)	*Bone age (years)*	*Calculated age for height (years)*	*Sex*
Bone age normal	19	19	12	F
	16	16	16	F
	15	15*	9	F
	14	14	11	F
	14	14	13	F
	14	14	13	F
	13	13	12	F
	12	12	11	F
	10	10	8	M
	9	9	9	F
	8	8	7	F
	7	7	7	M
	7	7	5	F
	6	6	6	F
Bone age retarded	14	11	9	M
	12	8	7	M
	12	8	9	M
	11	8	7	M
	10	8	6	M
	10	7	6	F
	9	7	6	M
	8	6	9	M

* Severe rickets.

Intestinal function. 1. *Output of fat in the faeces.* It is generally considered that in healthy children more than 90 per cent. of the dietary fat is absorbed. Cooke, Peeney, and Hawkins (1953) stated that $94{\cdot}6 \pm 1{\cdot}9$ per cent. of the dietary fat is absorbed by normal adults. Fat-balance studies were carried out in 11 children in the present series (Table II). The mean fat-absorption in these cases was 84 per cent.; in eight children fat-absorption was less than 90 per cent., and the figures in the remainder were 91 per cent., 91 per cent., and 90 per cent. respectively, that is at the lower limit of the normal range. For each of the other 20 children from whom stools were obtained, usually five-day collections, the daily output of fat is shown in Table II. It will be seen that the figures ranged

from 0·5 gm. to 14 gm. per day, with a mean of 6·5 gm. The corresponding figures in 20 normal controls ranged from 1·4 gm. to 4·6 gm. per day, with a mean of 2·7 gm. On average, the children who had had coeliac disease were thus still losing more than twice as much fat in the stools as normal children; this

TABLE II

Details of Fat-balance Studies and Faecal Fat Output in 32 Children who had had Coeliac Disease

Case number	*Age (years)*	*Sex*	*Fat-absorption (%)*	*Days of balance*	*Daily excretion of fat (gm.)*
1	16	F	86	18	..
2	14	F	..	..	5·4
3	7	F	..	..	6·6
4	6	F	..	..	5·5
5	5	F	..	..	12·3
6	16	M	..	..	4·9
7	15	F	68	5	..
8	12	M	88	10	..
9	19	F	..	..	9·0
10	16	M	..	..	..
11	13	F	87	18	..
12	8	F	83	5	..
13	14	M	..	..	11·8
14	11	F	87	5	..
15	11	M	91	10	..
16	9	M	..	..	14·0
17	9	F	..	..	9·7
18	4	F	..	..	6·6
19	13	F	..	..	0·5
20	14	F	..	..	4·6
21	10	M	..	..	4·0
22	8	F	83	5	..
23	10	M	91	5	..
24	10	F	72	5	..
25	10	F	90	8	..
26	7	M	..	..	4·3
27	12	M	..	..	7·3
28	11	M	..	..	9·6
29	13	F	..	..	1·2
30	12	F	..	..	5·6
31	14	F	..	..	3·2
32	8	M	..	..	4·4
		Mean	84%		6·5 gm.

increase in the fat-content of their stools over the normal is highly significant ($P < 0.0001$).

2. *Absorption in the upper small intestine, judged by the oral glucose-tolerance test.* An increase of over 40 mg. of glucose per 100 ml. above the fasting level in the blood was considered normal. According to this criterion only six patients showed normal figures. It must be remembered, however, that oral glucose-tolerance tests may occasionally give misleading information on intestinal absorption, either because of variable gastric emptying or because of rapid utilization of blood-sugar.

3. *Radiography of the small intestine.* Frazer, French, and Thompson (1949) have demonstrated that the introduction of fatty acids to the small intestine

causes a clumped or flocculated radiographic pattern in normal subjects examined with a simple aqueous barium-sulphate suspension. They have also been able to produce a similar pattern *in vitro* by mixing this contrast medium with alimentary mucus. They have therefore postulated that the clumped pattern observed in the adult sprue syndrome is due to the flocculating effect of an excessive secretion of mucus, induced by the abnormal contents of the

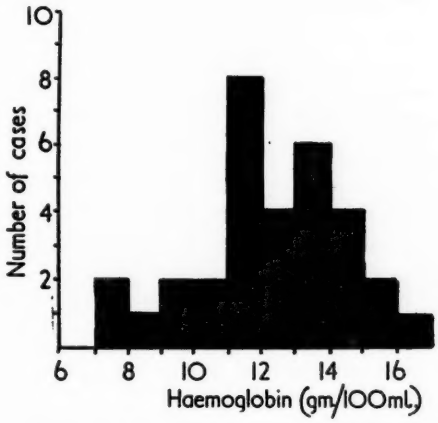

FIG. 2. Haemoglobin levels in 32 children who had had coeliac disease.

bowel. In the present series a simple barium suspension was clumped in all but one of 30 children examined; in 50 per cent. the clumping was gross. These findings, however, are not significant, for clumping occurs in a high proportion of normal children (Astley and Gerrard, 1954). Certain complex barium-sulphate preparations resist the clumping effect of mucus (Ardran, French, and Mucklow, 1950; Astley and French, 1951). With these preparations the anatomical detail of the bowel can be more clearly visualized, and it is found to be dilated both in the adult sprue syndrome (French, 1952) and in coeliac disease (Anderson, Astley, French, and Gerrard, 1952). The dilatation decreases or disappears during recovery, but reappears in relapse. In the present series some degree of small-intestinal dilatation was present in 22 of the 30 patients examined; it was slight in six, considerable in 10, and gross in six. A more detailed analysis is given elsewhere (Astley and Gerrard, 1954).

Haematology. The distribution of the haemoglobin values is given in Fig. 2, from which it will be seen that in 19 cases the haemoglobin was less than 13 gm. per 100 ml. The two lowest values were 7·1 and 7·3 gm. per 100 ml.; the last value was obtained from a girl who had collapsed at work on account of her anaemia and was recuperating at home when reviewed. The packed cell volume was less than 36 per cent. in 12 cases, the mean corpuscular volume less than 80 c.μ in 28, and the mean corpuscular haemoglobin concentration less than 33 per cent. in 14. These figures show that an appreciable iron-deficiency

anaemia was present in the majority of the patients: none had a macrocytic anaemia.

Conclusion. An analysis of the clinical, biochemical, and radiological findings revealed that there was not one of the patients reviewed who was normal in every respect. No patient was completely free from symptoms, nor were any desperately ill, but they were on average 12 per cent. under-weight, 7 per cent. under-height, and a little anaemic, with the mean haemoglobin 11·8 gm. per 100 ml., and they were losing 16 per cent. or 6·5 gm. of the dietary fat in the stools each day. In this context it should be noted that steatorrhoea in older children is not always associated with diarrhoea; most of the stools of the older coeliac patients examined by us were normal in colour and consistency in spite of their high fat-content.

Discussion

Although Hardwick (1939) concluded that many children with coeliac disease made a complete recovery and were able to tolerate normal diets, the present survey has shown that signs and symptoms of coeliac disease may persist for many years in children who have not been maintained on a diet free from wheat gluten. This result is in keeping with the findings of Sant'Agnese (1953); he re-examined 23 children diagnosed several years before as suffering from coeliac disease, and found that many still exhibited radiological and biochemical abnormalities, and that 10 were still excreting more than 4 gm. of fat per day. The frequency of latent abnormalities in coeliac disease was noted by Parsons (1932), who found that apparent clinical cure was often associated with excessive excretion of fat in the stools. Further, it appears from the studies of Bennett, Hunter, and Vaughan (1932), and of Cooke, Peeney, and Hawkins (1953), that symptoms may remain latent for many years, and then flare up in later life. Thus, of 100 cases of adult steatorrhoea examined by Cooke and his colleagues, symptoms dated from childhood in 43. Zellweger and Lauchli (1950) re-examined 22 adults known to have had coeliac disease in childhood. They found that several still had minor disturbances of bowel function and intolerance of fat; one of the two patients who had severe symptoms had developed the classical form of non-tropical sprue. From these findings and from the present study it appears that the former treatment of coeliac disease with fat-restricted diets containing variable amounts of wheat gluten frequently resulted in retarded development, and sometimes resulted in the persistence of signs and symptoms of steatorrhoea into adult life. It is possible that clinical recovery may have occurred on these diets, and this result would be expected if the alimentary tract can learn to handle gluten, but it must also be borne in mind that there is great variation from child to child in the amount of bread ingested, and if a child with coeliac disease does not eat much food containing wheat flour he will appear to recover from his complaint, even though he may still be sensitive to gluten. One patient whom we have recently encountered, for example, who had 'recovered' from coeliac disease, was not only of normal height and weight,

but was completely free from symptoms; this surprised us until we discovered that of his own accord he had always refused to eat bread, biscuits, and pastry.

Children with coeliac disease improve rapidly when treated with a wheat-gluten-free diet (Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952; Sheldon and Lawson, 1952); but this diet must be maintained if normal development is to be ensured, and complications such as nutritional anaemia, rickets, and tetany avoided. Moreover, the observation that some adults with steatorrhoea respond much less favourably than children with coeliac disease to a wheat-gluten-free diet (Anderson, Frazer, French, Hawkins, Ross, and Sammons, 1954) suggests that the disease process, if allowed to persist, may occasionally become irreversible. The severity of the initial symptoms in our experience bears no relation to the extent of the disability during the later course of the disease, and the removal of gluten from the diet requires to be as complete in patients with mild as in those with severe symptoms. One child, for example, whose initial symptoms were slight, and who remained free of them until the age of four years, was subsequently so severely affected that she developed rickets as well as a gross anaemia, and her physical development was so retarded that she was more under-weight and under-height than any other child in the series. It is not yet known for how long this gluten-free régime should be maintained, but, because we have not encountered a child, or even one of the nine adolescents, who was clinically and biochemically normal, and because the average rate of growth has been so appreciably and significantly reduced, we consider that ideally the gluten-free diet should be maintained until active growth has ceased. Whether it should persist thereafter will depend on whether steatorrhoea returns with the reintroduction of gluten.

We wish to thank the Consultant Staff of the Children's Hospital, Birmingham, for permission to study their patients, and Sisters N. Howells and J. Woodward, as well as their Nursing Staff, for invaluable help with the metabolic studies. We are very grateful to Dr. Charlotte Anderson for her help in initiating this work, to Dr. J. A. H. Waterhouse for undertaking the statistical analysis, and to Professor Frazer for his interest and encouragement. We are indebted to Mr. J. G. Williamson for the diagrams, and to Miss J. Kemp and Miss M. Cutler for technical assistance. Finally we gratefully acknowledge financial assistance from the United Birmingham Hospitals Research Fund, the Medical Research Council, and Messrs. Cow & Gate, Ltd.

Summary

Thirty-two patients, aged four to 19 years, who had been diagnosed as suffering from coeliac disease in early childhood, have been reassessed. They had all been maintained on a diet containing wheat gluten.

On clinical examination and inquiry not one appeared to have recovered completely; the commonest persisting symptom was a mild intermittent diarrhoea. The majority were below average in weight and height for their respective ages.

Biochemical, haematological, and radiological investigations confirmed the clinical impression that the coeliac disorder had persisted. Steatorrhoea, flat oral-glucose-tolerance curves, anaemia, and dilated small-intestinal patterns were found, singly or in combination, in all cases.

It is concluded that children with coeliac disease maintained on régimes which contain wheat gluten do not make a complete recovery. It is probable that optimal growth and health will only be achieved on a diet free from wheat gluten, which should be maintained at least until full maturity.

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POTASSIUM METABOLISM IN GASTROENTERITIS[1]

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(From The Hospital for Sick Children, Great Ormond Street)

With Plate 4

THE object of this paper is to draw attention to the association of abdominal distension and paralytic ileus in infants with gastroenteritis. The use of potassium in this disease will also be discussed, with emphasis on its value in the complications just mentioned and the precautions necessary in prescribing it. A preliminary report on ileus and hypokalaemia has already appeared (Schlesinger, 1953). Since the classical work of Darrow (1946), Govan and Darrow (1946), and Gamble (1951), much more attention has been paid to rehydration and rectification of electrolyte disturbances. This treatment has considerably reduced the mortality of gastroenteritis. For some time potassium depletion has been known to have a specially adverse effect, but all the clinical features are not yet sufficiently recognized. In surgical cases it is now generally agreed that abdominal distension or paralytic ileus is frequently accompanied by hypokalaemia (Randall, Habif, Lockwood, and Werner, 1949; Eliel, Pearson, and Rawson, 1950), and that additional potassium in the period following operation may reduce the risk of this serious complication, or help to cure it once it has occurred. There are very few references to the condition in infantile gastroenteritis (Williams, 1952), and after discovering several striking instances we thought a more extensive study advisable. From 1948 to 1951 653 infants with gastroenteritis, admitted to a special unit at the Hospital for Sick Children, Great Ormond Street, were studied. Clinical and biochemical aspects of abdominal distension were investigated and, later, the close relationship of hyper- and hypokalaemia in gastroenteritis, and its direct bearing on the timing of replacement therapy. With this object in mind serum-potassium levels were estimated in all severe cases as a guide to subsequent treatment, instead of blindly using potassium-containing solutions, such as Darrow's and Butler's repair fluids. In the beginning of the series it was striking how often hyperkalaemia was found in the first blood analysis, at a time in fact when the infants were dehydrated. Hypokalaemia may develop only when dehydration has been rectified; the present policy therefore is to take blood samples only after rehydration has been accomplished.

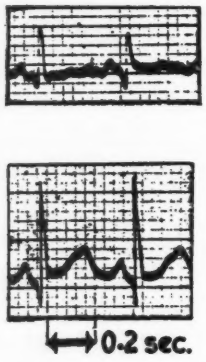
Investigations

Apart from the usual routine bacteriological investigations of the mouth or throat and the rectum in search of a specific organism, together with blood

[1] Received July 15, 1954.

counts and urine examination, particular attention was paid to the blood chemistry.

Biochemical investigations. One or more blood analyses were performed in the majority of infants who were severely affected. Plasma-bicarbonate and chloride, blood-urea, serum-proteins. and serum-potassium were estimated, the



(*a*) Serum-potassium 10·7 mg. per 100 ml. (2·7 mEq. per litre).

(*b*) 10 days later: serum-potassium 22·1 mg. per 100 ml. (5·6 mEq. per litre).

FIG. 1. Electrocardiographic tracings (standard lead II) showing flattening of T waves during hypokalaemia and return to normal with treatment.

last by a colorimetric method (Kramer and Tisdall, 1921), a normal level being taken as 16 to 22 mg. per 100 ml. (4·1 to 5·6 mEq. per litre).

Radiology. In difficult cases a plain X-ray of the abdomen was helpful in distinguishing between an organic obstruction and paralytic ileus. Presence of gas throughout the whole of the small intestine is certainly in favour of the latter diagnosis (Plate 4, Fig. 4). Fluid levels may suggest, but are not definite evidence of, organic obstruction, as they are also seen in simple gastroenteritis and in severe cases of coeliac disease, when they merely signify disturbance in intestinal motility.

Electrocardiography. Like other observers, we have found electrocardiographic changes in hypokalaemia, which disappeared when the serum level returned to normal (Fig. 1).

Clinical Picture

1. *Severe type. Paralytic ileus with distension* (seven cases, with three deaths). The most severe form of abdominal distension presented an alarming clinical picture. The infant, already very ill, became enormously distended, so that the skin of the abdominal wall was stretched and shiny. Sometimes distension developed in the course of a few hours and was sufficient to cause dyspnoea. Vomiting was severe, becoming bile-stained after a few hours. Copious diarrhoea was sometimes followed by a period during which no stools were passed. Once the distension was overcome, the infant began to pass numerous small, greenish-brown stools. An X-ray showed great dilatation of the whole of the small intestine and stomach, with numerous fluid levels. Seven patients of this type

were encountered, including one who was at first thought to be suffering from an organic intestinal obstruction. His case history (G. A.) is of considerable interest, and will be found in the Appendix. There were three deaths in this group; in two hypokalaemia appeared to be a contributory factor (Table II). A rough correlation between the degree of the distension and the severity of

TABLE I

Cases of Gastroenteritis with Distension, showing Important Features

Group	*Number of cases*	*Deaths*	*Vomiting*	*Evidence of obstruction*	*Average duration of distension in days*	*Oedema*	*Average serum-potassium*	
							mg./100 ml.	*mEq./l.*
Severe	7	3	5	7	6·5	5	10·7	2·6
Moderately severe . .	17	6	7	0	4·5	8	11·5	2·9
Mild	21	3	0	0	1	3	15·3	3·8

TABLE II

Causes of Death among Infants with Distension

Patient	*Distension*	*Hypokalaemia*	*Cause of death*	*Hypokalaemia a factor in causing death*
GROUP I. *Severe cases*:				
R. H.	++	+	? Ileus	Yes
M. E.	++	+	Cardiac failure	Yes
B. S.	++	+	Ileus. Marasmus	No
GROUP II. *Moderately severe cases*:				
C. T.	++	+	Suppurative thrombophlebitis	Yes
T. D.	+	+	Cardiac failure	Yes
R. B.	++	+	Osteomyelitis. Pyaemia	No
E. S.	+	+	Ulcerative enteritis and otitis media	No
D. B.	+	+	Marasmus	No
R. F.	+	+	Pyaemia	No
GROUP III. *Mild cases*:				
K. G.	+	+	Pulmonary and cerebral oedema	No
B. M.	+	+	Suppurative thrombophlebitis and otitis media	No
B. T.	+	+	Marasmus	No

the hypokalaemia was observed (Table I). All except one of the patients were oedematous, and all were alkalotic during the period of hypokalaemia.

2. *Moderately severe type. Persistent distension without ileus* (17 cases, with six deaths). Here there was no evidence of ileus or actual obstruction. The degree and duration of the distension varied considerably; in some instances there was no disturbance of feeding or evidence of discomfort. More commonly the abdomen was noticed to be tense and tympanitic; this was associated with reluctance over feeds, and sometimes with vomiting, but it was impossible to determine whether or not the vomiting was the result of the distension. Bile was not present in the vomit. The condition was not severe enough to need

gastric or duodenal suction, and the passage of a rectal tube was quite ineffective. There were six deaths, in two of which hypokalaemia and abdominal distension were considered important factors (Table II).

3. *Mild type. Transient distension* (21 cases, with three deaths). Included in this group are those cases in which the distension lasted for less than a day. It was not great, caused no difficulties in management, and required no special treatment. In 14 cases mild hypokalaemia was present; the remaining seven infants had normal or raised serum-potassium levels during the short period of distension. Death was unconnected with this brief complication (Table II).

Relationship of Serum-Potassium Level and Distension

Analysis of the blood chemistry in the 653 cases shows that hypokalaemia was present at some stage in 67 patients, and was associated with abdominal distension in 37. Distension occurred in only eight children who had a normal

TABLE III

Frequency of Hypokalaemia and Distension or Ileus

	Distension	*No distension*
Hypokalaemia present . .	37	30
Hypokalaemia absent . .	8	578
Total	45	608

or raised serum-potassium level, and in them it was minimal (Table III). There was no set time for the appearance of hypokalaemia, although it seemed to be roughly related to the severity and duration of the diarrhoea. When a series of serum-potassium estimations was carried out in the same infant, abdominal distension followed soon after low levels were reached, but occasionally remained some days after it had risen to normal (Fig. 2). The fall in the serum-potassium level also varied considerably, but in no case did it drop below 6·5 mg. per 100 ml. (1·7 mEq. per litre). An exact relationship between the degree of hypokalaemia and the severity of the abdominal distension cannot be demonstrated, but the distribution of cases (Fig. 3) suggests that 12 mg. per 100 ml. (3·1 mEq. per litre) is a critical level. Statements in surgical reports have implied that distension or ileus, with its associated vomiting, may well be the cause rather than the result of hypokalaemia. This seems unlikely, as in our series hypokalaemia was commoner than abdominal distension and usually preceded it by a few days. In 19 cases in which the spacing of blood samples allowed the duration of hypokalaemia to be assessed with reasonable accuracy, it appeared to have lasted for an average of 5·4 days in 13 distended infants and 3·3 days in six who had no distension.

To summarize the results of the investigations just described, it seems that abdominal distension in gastroenteritis (and with it the risk of ileus) is the direct result of potassium depletion which immediately precedes it. Furthermore, the condition is most likely to arise when potassium loss has been particularly heavy and prolonged.

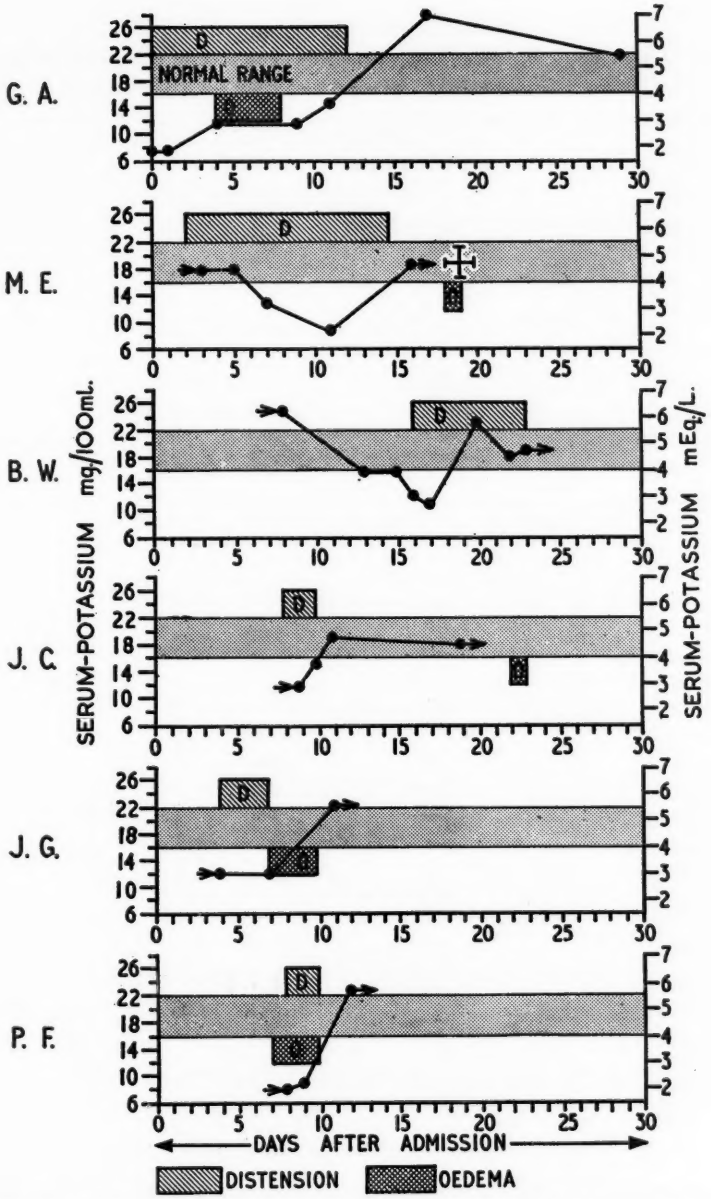


FIG. 2. Serial serum-potassium estimations in six infants with gastroenteritis, showing the relationship between hypokalaemia, distension, and oedema. Note that in patient B. W. the distension persisted for four days after the serum-potassium had become normal.

Diagnosis

1. *Severe cases* (*Paralytic ileus with distension*). The diagnosis is rarely in doubt if this complication arises in a known case of gastroenteritis, but difficulties may occur when an infant is first seen with distension and bilious vomit-

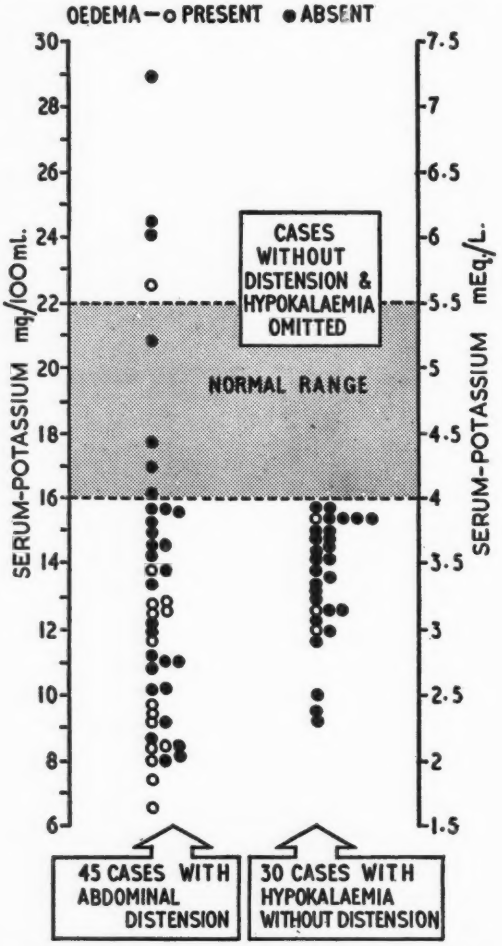


FIG. 3. Diagram showing that abdominal distension or ileus occurred in most of the patients with a serum-potassium level below 12 mg. per 100 ml. (3·1 mEq. per litre), although these complications also appeared with less severe degrees of hypokalaemia.

ing, without any clear previous history of diarrhoea (see Appendix). Careful inquiry may reveal a history of looseness of the stools before the onset of distension, in which case a watery offensive motion typical of gastroenteritis may follow rectal examination. It is not always easy, however, to decide

whether there is an organic obstruction of the bowel, and this must be carefully excluded. Simple X-ray films of the abdomen without barium have already been mentioned as being of some diagnostic value, but even these can be fallacious.

2. *Distension without ileus.* There are three conditions commonly associated with abdominal distension which are liable to produce attacks of diarrhoea and vomiting. One, somewhat loosely termed marasmus, is the most important. Here the infant, usually under six months of age, is grossly under-weight, with loss of fat from the cheeks and subcutaneous tissues. There is a history of failure to gain weight for some months, followed by actual loss in weight; the onset is sometimes preceded by an attack of gastroenteritis, and recovery, when it occurs, is very slow, with frequent relapses. Abdominal distension in marasmus does not appear to be connected with potassium deficiency, but is probably due to general wasting of the muscle of the bowel and abdominal wall. *Post mortem* the small intestine, in particular, is usually very thin and distended with gas. The cause of the condition is still in doubt. Infants suffering from coeliac disease or from fibrocystic disease of the pancreas are also liable to develop gastroenteritis and, with their abdominal distension, offer further difficulty in diagnosis.

Complications

1. *Oedema.* There appears to be a definite relationship between oedema and hypokalaemia. Oedema occurred in 18 of the 67 hypokalaemic infants, and was associated with the lowest serum-potassium levels (Table IV). Sixteen of these 18 infants also had abdominal distension. The cause of the oedema is not entirely clear, but will be discussed later. It was certainly not due to therapeutic overhydration, which was always carefully checked.

2. *Disturbances of acid-base balance* seemed to follow a fairly constant pattern (Table V). In infants seen early in the illness, who had been treated at the most with simple rehydration, the plasma-bicarbonate was low or normal. The serum-potassium level varied considerably in different patients, low rather than high figures being common. Infants seen at a later stage, who had also received no treatment beyond, perhaps, simple rehydration, were more often found to have hypokalaemia, with a normal or high level of plasma-bicarbonate. This tendency was, however, most marked in infants who had received prolonged treatment with repair solutions containing little or no potassium, such as plasma, blood, Hartmann's solution, or glucose saline. Acidosis in this last group was rare, and alkalosis was usually present.

3. *Liver failure.* Nine patients had enlargement of the liver, with or without jaundice and other evidence of hepatic insufficiency (Schlesinger, Payne, and Burnard, 1949).

4. *Hyperkalaemia* was found at some stage of the disease in 29 of the 653 children; many of these became hypokalaemic later. In the majority the raised serum-potassium level was discovered on the day of admission to hospital, with dehydration and an increased blood-urea. Nine had had no additional

potassium (Table VI); the remaining 20 had received extra potassium, 10 while still in a dehydrated state.[2] There were seven deaths in this group, at least two of which were probably due to cardiac arrest (Table VII). One infant (D. M.-H.) had a 2:1 heart-block before she died.

TABLE IV

Relationship between Hypokalaemia, Oedema, and Plasma-Bicarbonate

	Number of cases	Average serum-potassium		Average plasma-bicarbonate	
		mg./100 ml.	mEq./l.	CO_2 vols. %	mEq/l.
Oedema	18	11·3	2·9	53·0	23·7
No oedema	49	13·0	3·3	47·0	20·9
All cases	67	12·5	3·2	49·0	21·9

TABLE V

Relationship of High and Low Serum-Potassium Levels to Acid-Base Balance and Stage of Disease

		Without treatment				After treatment (excluding patients treated with sodium lactate or potassium salts)	
		Early cases (within 5 days of onset of symptoms)		Late cases (over 5 days from onset of symptoms)			
Serum-potassium		Low	High	Low	High	Low	High
Plasma-bicarbonate	Low	8	5	0	0	3	1
	Normal	9	4	7	0	12	0
	High	0	0	6	0	10*	0

* In two additional cases a low serum-potassium level occurred after giving sodium lactate.

Treatment

Hypokalaemia. It is now clear why additional potassium should never be given to dehydrated infants with gastroenteritis, except in the small quantity contained in Hartmann's solution or human plasma. When rehydration is progressing favourably potassium can be safely introduced. The dosage usually adopted over the 24 hours was one to two gm. of potassium chloride given orally, or half to one gm. in the intravenous fluids, depending on the degree of hypokalaemia. Potassium can be prescribed prophylactically for all severely ill infants for four or five days, as soon as dehydration has been overcome. Watch is kept on the patient's progress, and if the stools remain loose the amount of potassium may have to be increased to make good the loss from prolonged diarrhoea. It is usually necessary to continue oral potassium until the infant is given milk feeds, but the same care is required, and treatment must be interrupted in the event of renewed dehydration with an acute relapse. Throughout treatment it is best to check serum-potassium levels, and to be guided by the results of these tests. In the event of hyperkalaemia all additional potassium

[2] In the early cases of this series potassium citrate was given as a precautionary measure against crystalluria when sulphonamides were prescribed. This practice was later abandoned.

is stopped and rehydration assured. Clinical evidence of hyperkalaemia, such as bradycardia and heart-block, is rare, and death is usually due to sudden cardiac arrest. Nevertheless paralysis has been described by Bull, Carter, and Lowe (1953), and they recommended insulin and glucose as emergency treatment and cation-exchange resins for more prolonged therapy.

Distension and ileus. If hypokalaemia can be avoided, abdominal distension and ileus are unlikely to occur. Nevertheless occasional cases will arise and

TABLE VI

Hyperkalaemia without Additional Potassium Therapy

	Highest serum-potassium level		*Serum-sodium*					
Patient	*mg./100 ml.*	*mEq./l.*	*mg./100 ml.*	*mEq./l.*	*Acid-base balance*	*Blood-urea (mg./100 ml.)*	*Dehydration*	*Result*
S. C.	29·0	7·4	..	..	Acidosis	25	+	Recovery
I. L.	27·0	6·9	..	..	,,	38	+	,,
M. L.	26·0	6·7	..	..	,,	46	+	,,
T. K.	24·7	6·3	442	192	,,	..	++	,,
W. M.	24·5	6·3	405	176	,,	78	+	,,
R. A.	24·0	6·2	..	..	Normal	76	+	,,
B. C.	23·7	6·1	..	..	,,	40	0	,,
N. A.	23·1	5·9	..	..	,,	40	±	,,
C. H.	23·0	5·9	..	..	Acidosis	148	++	,,

TABLE VII

Hyperkalaemia after Additional Potassium Therapy

	Highest serum-potassium level					
Patient	*mg./100 ml.*	*mEq./l.*	*Blood-urea (mg./100 ml.)*	*Heart*	*Complications*	*Result*
D. M.-H.	30·2	7·7	44	2:1 block	Nephrocalcinosis	Sudden death
J. G.	24·5	6·3	302	..	Anuria	,,
G. T.*	43·0	11·0	83	..	..	,,

* This case occurred in 1947, and is included because of the exceptionally high level of serum-potassium.

require urgent measures. Moderate abdominal distension needs no special treatment other than additional potassium, but it may be necessary to stop oral feeds for a while if vomiting occurs, and to rely instead on parenteral fluids. In severe cases with bilious vomiting nothing should be given by mouth, as attempts to persevere with feeds will make matters worse. A Ryle's tube should be passed into the stomach and the gastric contents aspirated. The tube is allowed to pass into the duodenum if possible, and continuous or hourly suction is started. It is important to measure the amount of fluid aspirated each day, and to allow for this amount when calculating the quantity of intravenous fluid required. Passage of a rectal tube is not usually of much help, as the gaseous distension is mainly in the small intestine. After 24 to 48 hours' suction the abdominal distension usually begins to subside, provided hypokalaemia has been overcome, and the fluid aspirated changes from the murky dark-green or brownish fluid of intestinal obstruction to the clear yellow-brown of normal duodenal juice. At

this stage small amounts of fluid, or dilute feeds, may be given down the tube, and suction is stopped for one or two hours to permit their digestion and absorption. If the distension does not recur, larger quantities may be given and the Ryle's tube removed. The presence of a tube in the stomach may have the undesirable effect of increasing gastric secretion and resultant loss of potassium (Ebrill and Naftalin, 1953). Some authorities therefore prefer intermittent intubation and suction.

Briefly summarized, the foregoing investigations have shown that 67 out of 653 infants with gastroenteritis had evidence of hypokalaemia at some stage of their illness. In 37 of these infants varying degrees of abdominal distension appeared, a serum-potassium level of 12 mg. per 100 ml. (3·1 mEq. per litre) being the critical level below which this complication was most likely to arise. In seven cases the infant's condition became very serious, and the clinical picture was that of paralytic ileus, simulating occasionally an organic intestinal obstruction. In the absence of hypokalaemia abdominal distension was uncommon; it was in fact only encountered in eight instances, in which it was mild, produced no symptoms, and required no treatment. Urgent measures, on the other hand, were necessary in the severe cases progressing to paralytic ileus. Gastric or duodenal suction was begun immediately, followed by intravenous potassium replacement as soon as rehydration had been satisfactorily accomplished. This treatment was continued until feeding was resumed, when further potassium, if required, was given orally.

Discussion

Various theories have been brought forward to explain the development of intestinal paralysis, gastric distension, and ileus under certain circumstances after surgical operation (Robineau, 1933; Lévy and Nora, 1935, 1946; Aird, 1949; Maingot, 1950). Potassium deficiency is now accepted as the major cause (Randall, Habif, Lockwood, and Werner, 1949; Darrow and Pratt, 1950; Eliel, Pearson, and Rawson, 1950), and this deficiency can act in the same way in diabetic coma (Nabarro, Spencer, and Stowers, 1952, *a*, *b*).

Potassium deficiency, acid-base balance, and oedema. Although hypokalaemia usually signifies a generalized potassium deficiency in the body, this is not always the case, as for instance in familial periodic paralysis (Talbott, 1941; Almaden, 1952), in which there is merely a shift of potassium from plasma to cells. Oral and intravenous increments of potassium will obviously tend to rectify a negative balance, whereas excessive amounts of water and sodium will increase potassium loss in the urine (Gamble, Wallace, Eliel, Holliday, Cushman, Appleton, Shenberg, and Piotti, 1951; Lans, Stein, and Meyer, 1952). Serum-potassium is also reduced by the administration of glucose in any quantity, since potassium leaves the circulation to be laid down with glycogen in the cells of the muscles and liver. This has a practical bearing on the type and amount of repair solutions used in treatment. With diarrhoea the losses are mainly from the bowel, though it is possible that in certain circumstances renal tubular

damage may follow severe dehydration and impair the power of the kidney to conserve potassium.

It has been shown that electrolyte disturbance in gastroenteritis generally follows a regular pattern. Early in the disease there is an acidosis, with a low plasma-bicarbonate and a high plasma-chloride level; the serum-potassium level may be high, normal, or low. With prolonged diarrhoea hypokalaemia is more apt to develop, and the acidosis will change to a mild alkalosis, often with hypochloraemia (see also Flett, Pratt, and Darrow, 1949; Fourman, 1954). This alkalosis also occurs in human dietetic experiments with a very low intake of potassium (Black, 1953). Here the explanation given was that the cellular potassium deficit was made good not only by extracellular $Na^{\cdot}$ ions but also by $H^{\cdot}$ ions, resulting in an alkalosis in the serum.

Black observed an expansion of extracellular fluid in one of his subjects, but there was no actual oedema; in Fourman's and Ainley-Walker's experiments (1952, 1954) oedema occurred. It has also been reported in potassium deficiency by others (Randall, Habif, Lockwood, and Werner, 1949; Eliel, Pearson, and Rawson, 1950). Black attributed expansion of the extracellular space to an excessive intake of sodium, and this is certainly a possible cause. Fourman (1954) took into account the fact that increase of extracellular fluid or oedema is usually a late phenomenon during the recovery period, when potassium is being restored to the cells. If urinary excretion of sodium is not increased at that time, an increase in extracellular fluid could be due to retention of sodium liberated from the cells as potassium entered them. In our own series oedema developed some days after hypokalaemia was first discovered, and may indeed have been brought about by a high sodium intake, such as is contained in Hartmann's repair solution and in plasma administered intravenously. Neither the oedema nor the alkalosis which accompanied it was severe, and this complication rarely called for special measures; nevertheless it might possibly have been avoided by giving more potassium and less sodium during that phase. Restriction of sodium intake may assume even greater importance in view of the experimental results of Cannon, Frazier, and Hughes (1953), which showed that excess of sodium in the presence of potassium deficiency damages the myocardium and liver-cells more severely than slight potassium deficiency alone.

Replacement therapy. From the balance data published by Darrow, Pratt, Flett, Gamble, and Wiese (1949) and Gamble (1951), a 10-lb. (4·5-kg.) infant with moderately severe gastroenteritis would be likely to have a potassium deficit of 40 mEq. (3 gm. KCl). Clearly this deficit is greater in severe or prolonged cases. Calculations based upon our two standard schedules for use with human milk or cow's milk, in which the amount and concentration of the milk are increased daily, indicate that during the first four days of treatment a 10-lb. (4·5-kg.) child would receive 22 mEq. K and 52 mEq. K respectively. These figures show that, in the average case, the potassium intake on a cow's milk schedule is adequate to replace the previous deficits during the first four days, but with human milk this would take six days. In uncomplicated acute cases,

without persistent diarrhoea, this rate of replacement is probably sufficiently rapid, since Darrow and Pratt (1950) have shown that even in the best circumstances it is unlikely that full replacement will be achieved in less than six days. In the more severe cases, however, or in cases of prolonged diarrhoea, some potassium salt should be given after rehydration, in addition to that contained in the schedule feeds. This supplement should be maintained until a full diet is being taken, diarrhoea has ceased, and the serum-potassium level has remained normal for a week. Darrow (1948) advised a daily dosage of 3·5 mEq. K (0·26 gm. KCl) per kg., which would amount to approximately 1 gm. of potassium chloride for a 10-lb. (4·5-kg.) child. In our experience a total of 5 gm. of additional potassium chloride, given over four or five days, has usually been sufficient to bring the serum-potassium back to normal level, though occasionally we have had to give up to 2 gm. KCl daily to keep pace with losses from diarrhoea. It is also most important to omit all potassium supplements temporarily in the event of a sudden relapse with dehydration and oliguria. If these precautions are taken, frequent estimations of the serum-potassium are unnecessary in uncomplicated cases when the oral route is used, but if intravenous measures are required exact knowledge of the serum-potassium level before and after the infusion must be available in order to regulate further treatment.

The danger of hyperkalaemia. The present study has emphasized the importance of a temporary phase of hyperkalaemia, of which a number of instances have been shown to occur at the height of the illness. Normally the kidney excretes surplus potassium rapidly, but glomerular filtration is reduced by dehydration, and hyperkalaemia may develop even when extra potassium salts have not been given (Darrow and Pratt, 1950; Almaden, 1952). Dangerously high levels may therefore occur if additional potassium is used therapeutically at the wrong time. Our alarming experiences in this connexion have been described (Tables VI and VII), and the method of avoiding them has been specially emphasized. It is not the purpose of this paper to discuss further the general subject of potassium metabolism, which has been covered during recent years by a series of admirable reviews (Fenn, 1940; Hoffman, 1950; Danowski and Elkinton, 1951; Symposium on Potassium Metabolism, 1953; Sheppard, 1951; Almaden, 1952; Black, 1953; Graham, 1954).

Mechanism of distension. Increasing interest has arisen recently in the relationship of intestinal muscle function to the potassium level in the body. Most previous work was centred on voluntary muscle and the myocardium. Paralysis of *voluntary striated muscle* occurs in a number of conditions associated with hypokalaemia. In familial periodic paralysis there appears to be no intracellular deficiency, and hypokalaemia is produced by migration of potassium from extracellular fluid into the cells. The paralysis depends entirely upon the level of serum-potassium, and is thought to be due to failure of conduction at the neuromuscular junction (Fenn, 1940). Similar paralysis has been described during recovery from diabetic coma (Holler, 1946), in the sprue syndrome (Harrison, Harrison, Tompsett, and Barr, 1947), and in certain types of nephritis (Brown, Currens, and Marchand, 1944). In these last three conditions there is

considerable intracellular as well as extracellular deficiency, so that it is not easy to raise the serum-potassium level, or to relieve the paralysis, by the small amount of potassium salt that proves so effective in familial periodic paralysis.

Cardiac muscle may suffer in two ways. A fall in the level of serum-potassium alone almost certainly produces the characteristic electrocardiographic changes, identical with those of familial periodic paralysis (Butcher, Wakim, Essex, Pruitt, and Burchell, 1952; Stewart, Smith, and Milhorat, 1940). An isolated heart placed in a potassium-free medium ceases to beat before any alteration of intracellular potassium has occurred (Butcher, Wakim, Essex, Pruitt, and Burchell, 1952), and it is possible that this asystole is brought about by some disturbance in conduction of the impulse. On the other hand the myocardium in heart failure from any cause is found to have a reduced amount of intracellular potassium (Fenn, 1940), and the same cellular depletion, with corresponding histological changes, has been shown to occur in heart muscle brought into failure experimentally by depriving the animal of potassium (Meyer, Grunert, Zepplin, Grummer, Bohstedt, and Phillips, 1950; Cannon, Frazier, and Hughes, 1953). Skeletal muscle is known to liberate potassium from the cells into the surrounding fluid with each contraction (Fenn and Cobb, 1936). Cardiac muscle no doubt does the same (Clark, 1921), and when surrounded by a medium poor in potassium, as in hypokalaemia from any cause, is unable to rebuild its cellular potassium-content against too steep a concentration gradient, and therefore fails.

Consideration of *intestinal muscular* movement and tone in relation to potassium deficiency reveals a number of discrepancies, and study of the normal physiology of gut motility has been hampered by the difficulty of separating the muscle from its nerve plexuses. Certain facts are known. Electrolyte variations in the intestinal contents have practically no effect on intestinal movement, provided the mucous membrane remains intact (Magee and Southgate, 1929–30), but reduction in the potassium level of the fluid surrounding a length of isolated rabbit jejunum causes an almost immediate diminution of its contractions, but no loss of tone (Magee and Reid, 1927). This effect is considered to be too rapid to be due to loss of intracellular potassium, and quite different from the gross intestinal dilatation and ileus which can be experimentally produced in an intact animal by depriving it of potassium (Winter, Hoff, and Dso, 1949; Webster, Henrikson, and Currie, 1950; Henrikson, 1951). Although in all these experiments the serum-potassium was reduced, and the ileus could be overcome by administering potassium, these changes of intestinal function have now been shown to be the result of rapid loss of intracellular potassium, and not directly related to any extracellular deficiency (Streeten and Vaughan Williams, 1952). The site of this loss is more difficult to determine in man. Considerable potassium deficiency has become established when ileus develops. In our cases the severity of this complication bore some relationship to the serum-potassium level, but this is not always the case (Streeten and Ward-McQuaid, 1952). There is good reason to believe that in severe gastroenteritis the deficit is in the cells (Darrow, 1946), and consequently that the abdominal

distension or ileus results from this deficit rather than from hypokalaemia alone. This would explain why in our patients the complication often persisted for some days after the serum-potassium level had returned to normal.

Summarizing all the available evidence, we believe that, whereas skeletal muscular power may be impaired by hypokalaemia alone, and cardiac muscular contraction is affected by both extracellular and intracellular potassium deficiency, the normal function of intestinal muscle is impaired only when intracellular potassium is depleted. If the potassium level in the serum is low, so that the cellular deficit cannot be replaced, each muscular contraction will cause progressive loss, and paralysis, distension, and finally ileus will supervene.

APPENDIX

Case History (see Fig. 2 and Plate 4, Fig. 4)

G. A., admitted at the age of 3 months.

History. At birth he weighed 10 lb. He was breast-fed for two weeks, then weaned because of maternal puerperal psychosis. After this he was sent to a residential nursery, where he developed gastroenteritis. There was an indefinite history of refusal of feeds, vomiting, and loose stools. On the day of admission to hospital he had frequent bile-stained vomits. During his three weeks in the nursery his weight had fallen from 12 lb. 8 oz. to 11 lb. 6 oz. Before admission to hospital he had been treated with saline and barley water by mouth.

On admission he was a wasted, dehydrated, and slightly cyanotic infant, with considerable dyspnoea from an enormously distended abdomen. No peristalsis was seen, but bowel sounds were heard. The liver edge was palpable about half a finger's breadth below the costal margin. On rectal examination some watery yellowish faeces followed the withdrawal of the finger.

Investigations. X-ray of the abdomen (Plate 4, Fig. 4) showed very marked distension of the small intestine, with numerous fluid levels. The large and small intestine both contained gas, and there was no evidence of an organic obstruction. The blood chemistry (on admission) was as follows: plasma-bicarbonate: CO_2 28·0 vols. per cent. (12·5 mEq. per litre); plasma-chlorides 729 mg. per 100 ml. as NaCl (135 mEq. per litre); serum-potassium 7·7 mg. per 100 ml. (1·9 mEq. per litre); serum-protein 4·8 gm. per 100 ml. The urine on admission (pH 5·0) contained five to 10 red blood-cells per high-power field, protein 40 mg. per 100 ml., an occasional granular cast, and chlorides 911 mg. per 100 ml. as NaCl (156 mEq. per litre). A rectal swab showed no pathogenic organisms; a throat swab yielded *Ps. pyocyanea*; no organisms were obtained from blood culture.

Progress. An intravenous drip was set up and 160 ml. of 1/6 molar sodium lactate were given, followed by half-strength Hartmann's solution. A stomach tube was passed and large quantities of greenish-brown fluid were aspirated. As soon as the result of the serum-potassium estimation was obtained and dehydration had been rectified, additional potassium chloride was given intravenously, and later by mouth. On the third day there was oedema, and the patient was given plasma intravenously. By the 12th day there was no abdominal distension or oedema. Oral feeds were started, and he appeared to be recovering, but at this time he was found to have evidence of tubular insufficiency (lower nephron nephrosis), with polyuria, albuminuria, and amino-

aciduria. He finally made a complete recovery, and was discharged weighing 14 lb., after 50 days in hospital.

Summary

1. Evidence has been produced of a direct relationship between abdominal distension and potassium deficiency in infantile gastroenteritis. In severe cases this distension may proceed further to paralytic ileus.

2. These complications can be prevented by providing an adequate intake of potassium. Once either condition has become established an increased intake of potassium is required.

3. Since transient hyperkalaemia so often exists in the stage of dehydration, administration of potassium salts should be delayed until the dehydration has been rectified.

4. It appears that intestinal muscular paralysis in these complications is more likely to be due to a cellular potassium deficit than to hypokalaemia alone.

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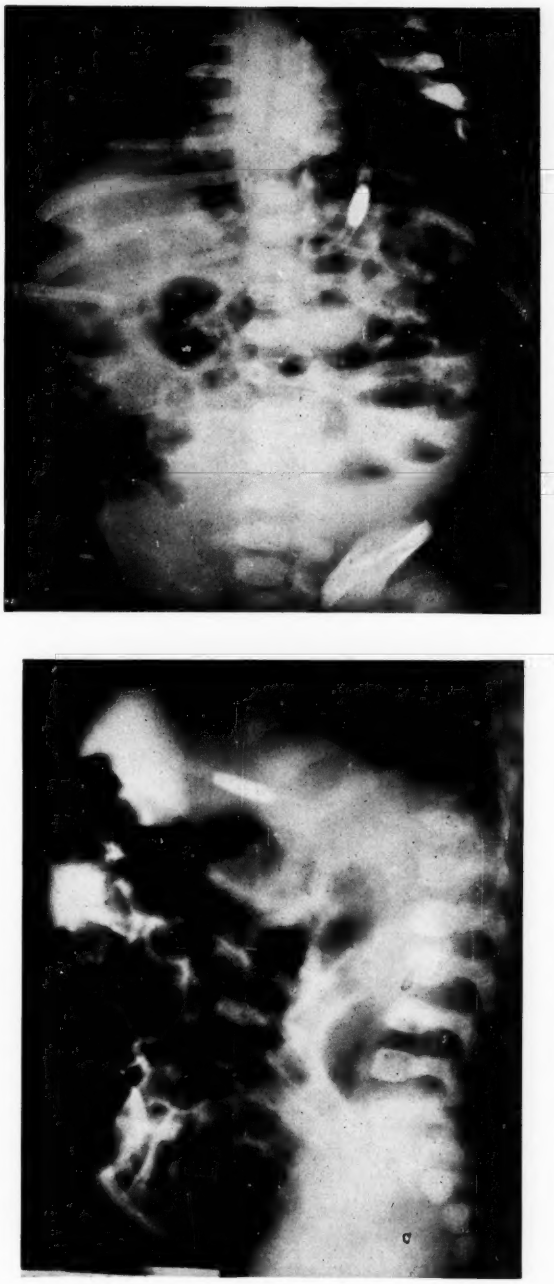

FIG. 4. X-rays of patient G. A. with paralytic ileus, showing gross intestinal distension with fluid levels

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THE KVEIM TEST IN SARCOIDOSIS[1]

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With Plates 5 and 6

On the hypothesis that sarcoidosis, like lymphogranuloma, might be a virus disease, Williams and Nickerson (1935) employed a skin test for its diagnosis. A piece of skin sarcoid tissue, suspended in six times its volume of normal saline, was sterilized by heat, and 0·05 ml. of this material was injected intradermally into each of four patients with suspected sarcoidosis and four normal control subjects. Within 24 hours a firm red papule was observed in the first group, and was still present a week later, whereas such a reaction was not observed in the control group. The histology of these papules was not studied; this important additional observation was provided by Kveim (1941). By means of intracutaneous inoculations of a heat-killed suspension of a sarcoid lymph-node, he obtained, in one to four weeks, lesions histologically consistent with sarcoidosis in 12 of 13 patients with sarcoidosis. Simultaneous control injections of Frei antigen and tuberculin did not produce this response. Since this reaction did not occur in normal subjects, nor in patients with lupus vulgaris, he concluded that the papules were specific lesions due to an unknown agent, and that the test served to differentiate sarcoidosis from tuberculosis. Putkonen (1943) employed this test in 42 patients with proved sarcoidosis and in a number of control subjects. 'Positive' papules were obtained in 33 patients either within two weeks after injection or, in some cases, after one to two months. Putkonen observed that the test was invariably positive in patients with active cutaneous sarcoidosis, and negative when such skin lesions had healed; he concluded that a positive reaction was an index of activity. He stressed the fact that antigens varied in their potency, and considered those obtained from lymph-glands to be the strongest. The natural history of the developing Kveim reaction was studied by Danbolt and Nilssen (1945), who obtained a positive result in 34 of 36 patients with sarcoidosis, compared with a negative result in 68 control subjects. A papule appeared after a latent period of one to two weeks, and continued to develop until it reached a maximum after two months. The infiltration remained unchanged for several months before receding slowly. Nelson (1949) considered that the reaction was a useful index of activity. He observed positive results in 11 of 15 patients with active sarcoidosis; the result was negative in all nine patients who had healed or inactive disease. He also observed positive responses to the intradermal inoculation of normal human splenic tissue, and concluded that, although the response was specific to patients

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with sarcoidosis, it was not due to any specific property of the sarcoid tissue itself.

The nature and preparation of the antigen. The antigen is prepared by emulsifying sarcoid tissue in saline. Tissue from any source, including spleen, skin, or tonsil, can be used, but a sarcoid lymph-node is considered to produce the most potent antigen. It is a turbid, brown fluid containing gross particulate material; Nelson (1948) advised that it should be of this consistency, as otherwise it is ineffective. Danbolt (1951), from extensive experiments and long experience, agreed that the active principle follows the corpuscular elements of the mixture. It does not pass through a Berkefeld filter, and is insoluble in water and ether. It is not destroyed by boiling, although its potency is somewhat reduced. In the present series Kveim antigen from two sources has been employed. The original suspension, prepared from a sarcoid lymph-node, was kindly supplied by Dr. Carl T. Nelson of New York. It was supplemented by further material, obtained at the autopsy of a patient with proven sarcoidosis, and consisting of a sarcoid lymph-node made into a crude antigen as described by Nelson (1948). The material was ground with physiological saline in a dilution of 1:10 by wet weight of tissue. Aerobic and anaerobic cultures were made to ensure sterility, and some antigen was inoculated into a guinea-pig to ensure that it was free from tubercle bacilli. The decanted suspension was sterilized by heat at 56° C. for two hours on two successive days. The mixture was diluted with an equal quantity of saline, and phenol added as a preservative in a final concentration of 0·25 per cent. The antigen is therefore a heat-sterilized saline suspension of sarcoid tissue in a final dilution of 1:20.

Methods

The material was injected intradermally into the flexor aspect of the forearm in a dose of 0·2 ml. Because of the indolent nature of the response, the site was chosen carefully so that it could be recognized a month later in the negative cases. This was achieved by injecting it at a fixed distance from some convenient landmark, such as a mole or a freckle. It is necessary to use a wide-bore needle for the injection because of the highly particulate nature of the antigen. All patients were observed at least once a week, and more frequently if they were in-patients. Skin biopsy of the inoculation site was made in every case between four and six weeks after injection, and the biopsy material was examined histologically for the presence of typical sarcoid lesions. A result was considered to be positive only if there was unequivocal evidence of sarcoid tissue, as distinct from a foreign-body giant-cell reaction. In five cases serial biopsies from the same site were undertaken to assess progress and the results of treatment. The tissues excised were fixed in 10 per cent. formol saline and examined for the presence or absence of a visible dermal nodule. Sections were stained with haematoxylin and eosin, by reticulin staining, and by the Ziehl-Neelsen method. In only one instance was a culture made from the biopsy specimen before fixation, and this did not grow tubercle bacilli.

Patients Investigated

The series consists of 16 patients with sarcoidosis, 28 with tuberculosis, and 19 with a variety of other diseases.

1. *Sarcoidosis.* These patients presented clinical evidence of widely disseminated sarcoidosis involving many different systems. In five instances confirmatory histological evidence of sarcoidosis was provided by skin or lymph-node

TABLE I

Clinical and Radiological Involvement in Kveim-positive Patients

Systems involved	*Number of patients*	*Chest X-rays*	
		Hilar glands	*Pulmonary mottling*
Thorax	12	12	7
Skin: Erythema nodosum	6 (8)	8	2 (4)
Skin: Plaques	2 (8)		2 (4)
Eyes	5	5	5
Joints	3	3	0
Glands	2	2	1
Brain	1	1	1

TABLE II

Clinical Syndromes in Kveim-positive Patients

Presenting features	*Number of patients*	*Chest X-rays*	
		Hilar glands	*Lung involvement*
Erythema nodosum	4	4	2
Iridocyclitis	3	3	3
Erythema nodosum + iritis + arthritis	2	2	0
Dyspnoea, malaise	3	3	3
Total	12	12	8

biopsy performed elsewhere than at the Kveim site. In all patients, except one of the four who were Kveim-negative, there were characteristic combinations of clinical features permitting a confident clinical diagnosis. This was supported by characteristic changes in serial chest radiographs; a negative Mantoux reaction to a dilution of 1:100 was present in 14 of the 16 cases. The two patients who showed a positive Mantoux reaction reacted only to 1:100 old tuberculin, and were judged to have a low sensitivity.

In the 12 Kveim-positive patients the systems involved, in order of frequency, are shown in Table I. The clinical syndromes presented by these patients fell into four categories (Table II):

(1) Four cases of erythema nodosum with accompanying evidence of hilar lymphadenopathy. In two of these cases X-rays also showed symmetrical nodular infiltration of both lungs.

(2) In a further two cases of erythema nodosum there was bilateral iridocyclitis, polyarthritis, and hilar lymphadenopathy. Both these patients were febrile, and complained of painful, stiff, slightly swollen joints, so that the initial clinical impression was that of acute rheumatism. The fever and pain

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were not suppressed by salicylates, and there was no supporting cardiac or electrocardiographic evidence of rheumatic fever. The presence of hilar lymphadenopathy, the negative Mantoux reactions to a dilution of 1:100, and the subsequent development of widespread erythema nodosum and bilateral iridocyclitis were suggestive of sarcoidosis.

(3) There were three patients in whom iridocyclitis was accompanied by hilar lymphadenopathy, and X-rays showed symmetrical mottling in both lung fields. One of these patients also showed evidence of involvement of the central nervous system.

A 26-year-old man developed subacute meningoencephalitis, with a left facial weakness, and was found to have an increase in the cells of the cerebrospinal fluid. Tuberculosis and other meningeal infections were excluded, and a Mantoux test showed a negative reaction to a dilution of 1:100. The accompanying evidence of iridocyclitis, hilar lymphadenopathy, and progressive, symmetrical, and nodular mottling seen in X-rays of the lungs, was suggestive of sarcoidosis. The Kveim test provided supporting histological proof. The patient responded to a course of oral cortisone, isoniazid, and intramuscular streptomycin, becoming free from symptoms and able to return to work. Radiological evidence of pulmonary sarcoidosis remained unaltered. A second biopsy from the Kveim test site, after 10 weeks of treatment with cortisone, and while the patient was still receiving this drug, again showed sarcoid tissue histologically.

(4) In three patients increasing breathlessness and vague chest pains, with malaise, were the main features of pulmonary sarcoidosis. Serial chest radiographs were strongly suggestive of this disease. Two of these patients were medical practitioners.

A man of 30 years, whose Mantoux reaction was negative, had increasing malaise and breathlessness, and there was radiological evidence of diffuse nodular infiltration in both lung fields. A clinical diagnosis of sarcoidosis was made, and histological proof was sought by liver biopsy. A negative result by the latter procedure did not alter a firm clinical impression of sarcoidosis. Before embarking upon a course of cortisone, streptomycin, and isoniazid, a Kveim test was performed. This produced positive histological proof of the presence of sarcoidosis. A second biopsy at the Kveim test site, performed two months after commencing oral cortisone, still showed sarcoid tissue. Some evidence of healing was suggested by the presence of increased collagenous tissue in the second biopsy.

Another male medical practitioner, aged 26 years, with similar symptoms and radiological evidence of sarcoidosis, was anxious as to the possibility of Hodgkin's disease, which had been suggested to him. He was reluctant to have a liver biopsy performed, so instead a Kveim test was done. This provided histological evidence of sarcoidosis, which reassured him. Uneventful recovery has followed, with complete clearing of the lesions in serial chest radiographs.

In four patients who showed evidence of sarcoidosis the Kveim test was negative both clinically and histologically. One of these patients had erythema nodosum, hilar lymphadenopathy, and a positive Mantoux reaction to a dilution of 1:1000. She was treated with prolonged rest in bed and calciferol; the Kveim test was performed during convalescence, three months after her lesions had

disappeared. Another patient had a nodule removed from the naso-labial fold for cosmetic reasons. This proved to be sarcoid tissue histologically, although there was no other evidence of sarcoidosis. A Kveim test was negative two years after this operation, when there was neither clinical nor radiological evidence of sarcoidosis. The remaining two patients with negative Kveim tests had evidence of long-standing pulmonary fibrosis with chronic iridocyclitis. In all four cases the clinical evidence strongly suggested that the sarcoidosis was inactive.

2. *Tuberculosis.* There were 28 patients with tuberculosis varying in degree of activity; in 18 the disease was active, and in the other 10 it was controlled or quiescent after treatment.

3. *Other diseases.* Nineteen other patients were chosen as control subjects. They included patients suffering from various diseases, including carcinomatosis, Hodgkin's disease, lymphosarcoma, and pernicious anaemia, and also a group of healthy men in whom the Mantoux reaction was negative.

Results

1. *Clinical.* After the intradermal injection of 0·2 ml. of antigen there may be a temporary immediate reaction in normal persons, usually lasting a few hours, which is presumably due to the trauma of injection. It may even persist as an indurated area for a few days, but disappears completely by the end of one week. In patients with sarcoidosis a small dusky-red papule develops after a few days, and is present as a distinct palpable nodule at the end of one month. It is usually about 0·5 cm. in diameter, but occasionally larger. Its development is characteristically indolent; it may continue to develop, or persist, for several months. During this sluggish course the dusky-red colour may wax and wane in intensity. Patients in the present series have correlated these variations in the colour with exacerbations of their iridocyclitis and other symptoms of the disease. Most workers with long experience of this test consider the result to be positive if a papule, or an area of induration, occurs at the injection site and remains palpable for at least 60 days. In a review of the subject Danbolt (1951) considered the reaction to be positive if there is 'a marked and distinct papule after a month, and which persists distinctly for weeks and months'. If a papule was small and receding a month after injection, he recorded the reaction as negative. Dusky-red or bluish-red nodules, with an average diameter of 0·8 cm., raised above the skin surface, and easily visible, occurred in 12 of our 16 cases of sarcoidosis; in the remaining four patients there was no visible nor palpable reaction. In three of the 28 patients with tuberculosis a knot of tissue, about 0·3 cm. in diameter, was just palpable under the skin. These nodules had not shown the slowly progressive development of a dusky-red, easily visible papule, which was seen in the sarcoid cases, but rather the persistence of an area of induration since the time of injection. There was no visible or palpable reaction in the 19 patients who either had other diseases or were normal subjects.

2. *Histological.* The histological reactions observed were (1) the reaction in sarcoidosis (Plate 5, Figs. 1, 2, 3); (2) the reaction in tuberculosis (Plate 5, Fig. 4; Plate 6, Figs. 5, 6); (3) a foreign-body giant-cell reaction (Plate 6, Figs. 7, 8); and (4) a non-specific cellular reaction.

(1) *The reaction in sarcoidosis.* Of the 16 patients with clinical evidence of sarcoidosis, 12 yielded histological evidence of sarcoid tissue at the site of the Kveim test. The appearance of a positive reaction was essentially similar in all cases, and consisted of one or more cellular foci in the dermis. The depth of the lesion from the skin surface was variable; some cases showed exclusive involvement of the superficial dermis, while in others the lesion was confined to the deep dermis. In no case was the epidermis involved by the process, and the squamous epithelium remained histologically normal. The foci of sarcoid tissue in the dermis were rounded in contour, varying from 2 mm. to 5 mm. in diameter. These lesions did not contain blood-vessels, and large, pink-staining epithelioid cells formed the bulk of the structure. The epithelioid cells possessed a distinct cellular boundary, with abundant cytoplasm and vesicular nuclei. At the centre of the lesion, the cytoplasm of these cells showed a tendency to fuse together, with a loss of distinction of the cell-boundary and degeneration of the nuclei, so that a small central area of pink-staining granular material was found containing nuclear debris. This type of necrotic change was present in three of the 12 'positive' biopsy specimens. The necrosis was always small in extent, and remained restricted to the centre of the cellular lesion, with no involvement of the adjacent collagen, while reticulin stains showed persistence of fine fibrils passing through this central focus; this reticulin network is not preserved in tuberculous lesions. Giant cells were also visible in the foci. Most of these were of the Langhans type, with pink-staining cytoplasm and a peripheral distribution of the nuclei. Occasional giant cells of other types were encountered; a few contained three or four nuclei, due to aggregation of the epithelioid cells, while others were larger with more centrally-placed nuclei. A variable cellular response was seen surrounding this zone. Some examples showed a thin rim of lymphocytes framing the central reaction. The most usual response was a mixture of lymphocytes, histiocytes, and a few plasma cells; some cases showed eosinophils, but neutrophile polymorphonuclear leucocytes were sparse.

(2) *The reaction in tuberculosis.* Three biopsy specimens, all from patients with active tuberculosis, revealed a reaction which differed in histological detail from the sarcoid response. These examples showed foci in the dermis composed of epithelioid cells, giant cells, and lymphocytes, but with the added feature of conspicuous necrosis. In addition to the central fusion of the epithelioid cells, with a small necrotic focus, the necrotic reaction spread outside the cellular lesion to involve the adjacent collagenous tissue, which became degenerate and homogeneous, with loss of its normal reticular staining properties. Ziehl-Neelsen preparations did not reveal the presence of acid-alcohol-fast bacilli. This type of reaction, occurring in three of the 28 tuberculous patients, differed therefore from the lesions produced by injection of the Kveim antigen in patients

with sarcoidosis. Although basically similar in cytology, it is distinguishable both by the extent of the necrosis and by the disruption of the reticular network in the necrotic area.

(3) *A foreign-body giant-cell reaction.* This type of cellular response was found in three control cases. In the dermis there were focal collections of inflammatory cells, consisting of polymorphonuclear leucocytes, lymphocytes, and histiocytes, with prominent giant cells. The latter were of the foreign-body type, showing variation in size, an irregular outline, and a tendency to central distribution of the nuclei. In two examples foreign crystalline material was present in the cytoplasm of the giant cells; in the third the foreign material was surrounded by the giant cells. All the crystals were birefringent, but no additional investigations have been carried out to elucidate their nature. These examples were readily distinguished from a true sarcoid reaction; epithelioid cells were absent, the giant cells were not of the Langhans type, and polymorphonuclear leucocytes were abundant.

(4) *A non-specific cellular reaction.* Six cases showed a non-specific inflammatory cell response. This consisted of a predominantly lymphocytic infiltration in the superficial dermis. The reaction was focal in distribution, and greatest around hair follicles, with involvement of the sweat ducts to a lesser extent. The cellular infiltration was sparse, and no purulent or necrotic reaction was seen. The histological features did not indicate any specific lesion.

Apart from these four distinct types of reaction, the remaining 25 biopsies showed no histological response in the dermis, both epidermis and dermis remaining normal.

The Nature of the Reaction

Although the mechanism of the reaction is unknown, various theories have been postulated.

1. *The virus theory.* The test was initially introduced by Williams and Nickerson (1935) on the assumption that, if sarcoidosis were due to a virus, a skin test similar to the Frei reaction could be employed in its diagnosis. There is no good evidence to support the virus aetiology of sarcoidosis, and moreover the Kveim test would be difficult to explain on such a basis. The slowly developing response, measured over weeks rather than days, is unlike that evoked by a virus antigen, as in the Frei test for lymphogranuloma venereum.

2. *The isomorphic reaction.* Dermatologists are familiar with this phenomenon. Irritants applied to one part of the skin are liable to reproduce the lesion found in another part; in this way the lesions of lichen planus and of certain types of syphilis can be reproduced by non-specific irritation. The reaction is also the basis of the Koebner scratch phenomenon in psoriasis. In many respects the Kveim test resembles the isomorphic reaction; a specific cutaneous response follows a non-specific stimulus. If this were the explanation it would be difficult to understand why, apart from an emulsion of sarcoid tissue, tubercle bacilli, B.C.G. vaccine, and normal spleen are almost the only agents which have produced a positive Kveim reaction. Many other

substances injected into sarcoid patients have failed to provoke this response. The most obvious instance is tuberculin. In spite of innumerable observations of tuberculin responses in sarcoidosis, the development of sarcoid tissue at the site of such an injection is extremely rare.

3. *Tuberculophosphatide theory.* It is conceivable that the Kveim reagent contains a tuberculin-like substance. Such a theory would be acceptable to

TABLE III

Results of Kveim Test in Sarcoidosis and Other Diseases

		Positive results	
		Sarcoidosis	*Control cases*
Williams and Nickerson	(1935)	4/4	0/4
Kveim	(1941)	12/13	Unspecified number, negative
Putkonen	(1943)	33/42	0/65
Danbolt and Nilssen	(1945)	34/36	0/68
Nelson	(1949)	11/15 (active) 0/9 (inactive)	Unspecified number, negative
Present series		12/16	0/47

those who consider sarcoidosis and frank tuberculosis to be different phases of the same disease. It has been demonstrated in animals that a tuberculophosphatide fraction of tubercle bacilli is capable of provoking a reaction consisting of epithelioid cells and giant cells, somewhat similar to sarcoidosis (Sabin, Doan, and Forkner, 1930). This tuberculophosphatide was injected intradermally by Harrell (1944) in patients with tuberculosis, patients with sarcoidosis, and normal control subjects. There was no reaction in the sarcoidosis and control groups, although wheals occurred in the tuberculous groups. Killed tubercle bacilli, when injected intradermally in patients with sarcoidosis, produce a Kveim-like reaction (Warfvinge, 1945). It would be instructive to repeat these observations with various fractions of tubercle bacilli, and to note the clinical and histological response, over prolonged periods.

4. *Allergic theory.* If the Kveim test can be interpreted as the response to an injected allergen, it is more readily classed with the delayed type than with the immediate 'histamine' type of response, because of the slow insidious onset, the prolonged reaction, the lack of response of the lesion to antihistamines and adrenaline, and its occasional conversion to hyaline tissue by cortisone (James and Thomson, 1954). Delayed-type skin reactions are impaired in sarcoidosis, whereas the immediate histamine-like skin tests give normal results (Sones and Israel, 1954).

Specificity of the test. Although the pathogenesis of the lesion is conjectural, it is necessary for diagnostic purposes to decide whether the Kveim test is specific for sarcoidosis. From the reports of Scandinavian and other workers it is clear that the test has a high degree of specificity (Table III). Its specificity has been assailed on the grounds that patients with sarcoidosis may react in

similar fashion to injections of B.C.G. vaccine (Lemming, 1942), viable and killed tubercle bacilli (Warfvinge, 1943, 1945), gland tissue of lymphatic leukaemia (Lomholt, 1943), and even normal splenic tissue (Nelson, 1948). Even simple trauma, such as an abrasion, may heal in such patients with the production of sarcoid tissue in the scar. Such lack of specificity of the antigenic stimuli capable of producing positive Kveim lesions may be important in studying the pathogenesis of sarcoidosis, but does not detract from the diagnostic value of the test. These antigens produce sarcoid tissue only in patients with sarcoidosis, and have very rarely, if ever, caused it in patients with other diseases. Sarcoid tissue is preferred as antigen only because it produces positive results in sarcoid patients more consistently than other substances.

Discussion

The Kveim test afforded histological proof of sarcoidosis in 12 out of 16 cases of sarcoidosis. In all cases the clinical evidence was such that a confident diagnosis of disseminated sarcoidosis could be made. In 14 cases the Mantoux test gave a negative result in a dilution of 1:100. Whereas the test was positive in 75 per cent. of these cases of sarcoidosis, it was negative in 47 control subjects. In this control group there were six instances of non-specific inflammatory-cell response, and three of foreign-body giant-cell reaction. None of these reactions could be confused with sarcoidosis in its histological features, and in none was there clinical evidence of a nodule suggestive of a positive Kveim reaction. The lesions of greatest interest were those of a tuberculous reaction, occurring in three out of 28 cases of tuberculosis. A knot of tissue was palpable four weeks after injection, but it did not have the size or the livid hue of the positive Kveim reaction. Histologically it resembled tuberculous tissue, with extensive necrosis and loss of the reticulin network. Ziehl-Neelsen staining revealed no acid-fast bacilli. In one of these cases a culture was made from part of the biopsy specimen for tubercle bacilli, before formalin fixation, but no organisms were grown. Since these lesions differed only clinically and histologically from the positive Kveim test in intensity of reaction, it is interesting to consider their significance. Danbolt (1951) noted a similar response in two patients with pulmonary tuberculosis, but did not record any histological evidence to indicate whether the reactions were sarcoid or tuberculous. Schaumann and Seeberg (1948) considered that the only difference, in reactions to intradermal tuberculin, between patients with sarcoidosis and patients with tuberculosis, was one of intensity. In a very small series of cases they examined the Mantoux reaction, clinically and histologically, four to eight weeks after injection of 0·1 mg. of tuberculin. Although the results were clinically negative, three of four cases of sarcoidosis showed sarcoid lesions histologically. These lesions were distinct from the responses, with necrosis and marked lymphocytic infiltration, noted in cases of tuberculosis. They suggested the possibility that the Kveim antigen contains a tuberculin-like substance, and that the different responses evoked by it in sarcoidosis and tuberculosis represent different expressions of tuberculous allergy. They supported the specificity of this response in sarcoidosis by

experiments in which other antigens were used intradermally in patients with sarcoidosis; with these skin irritants they were unable to produce sarcoid tissue.

When there is a conveniently accessible lymph-node or an area of sarcoidosis in the skin, this usually provides histological proof without resorting to the Kveim test. When such tissue is not available it is common practice to perform aspiration liver biopsy in an effort to obtain positive histological evidence of sarcoidosis. The Kveim test is an easier alternative, applicable to out-patients; it gives positive results frequently, and also serves as an index of activity and of the progress of the disease. The value of the Kveim test as an index of activity has been stressed by Putkonen (1943), Nelson (1949), and Nitter (1953), and has been confirmed in the present series. As an index of the progress of the lesion, the Kveim test site provides an obvious area of sarcoid tissue. Patients have noted that the lesion becomes dusky-red, livid, and tense during exacerbations of the symptoms of iridocyclitis, dyspnoea, and malaise, whereas it is pale and atrophic when they are enjoying a remission of the disease. Serial biopsies can be undertaken conveniently from the test site to evaluate the results of various treatments. In two cases in the present series serial biopsy was performed eight and ten weeks after the commencement, and during continuance, of treatment with combined oral cortisone, streptomycin, and isoniazid, and in each case sarcoid tissue was still obtained. In another three cases a second biopsy was performed six months to one year later, when the signs of sarcoidosis had subsided clinically and radiologically, and no histological evidence of sarcoid tissue was obtained at the Kveim site. In our present imperfect state of knowledge of the aetiology, natural history, and treatment of sarcoidosis, such a test provides useful practical information, and may also contribute to our knowledge of the pathogenesis of the disease. In the future it may be superseded by more accurate and quantitative serological tests, or even by the discovery of the cause of sarcoidosis, but until such time it should be retained as a useful adjunct to diagnosis.

We wish to thank the physicians who provided access to patients under their care, Dr. Carl T. Nelson for the original supply of Kveim antigen, and Dr. R. E. M. Thompson for assistance in preparing further material.

Summary

1. The Kveim test consists of the intradermal injection of a saline emulsion of sarcoid tissue. In patients with active sarcoidosis a dusky-red nodule develops insidiously at the injection site during the ensuing weeks. Histological examination of the nodule reveals characteristic sarcoid tissue.

2. The test was positive clinically and histologically in 12 out of 16 cases of sarcoidosis. It was negative in 28 patients with tuberculosis and in 19 patients with other diseases.

3. The nature of the reaction and the specificity of the test are discussed.

4. In the absence of easily accessible lesions for biopsy, the Kveim test is a simple, safe, and specific out-patient technique for providing (1) histological

proof of sarcoidosis; (2) an index of activity; (3) an index of the progress of the disease; (4) by serial biopsy, a method of evaluating various treatments.

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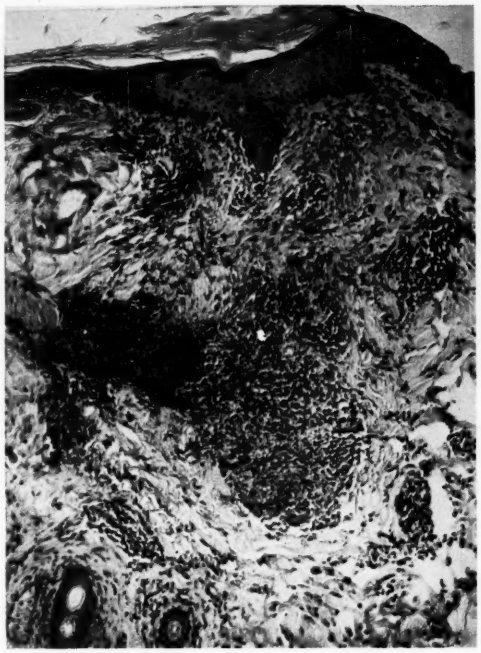

FIG. 1. Showing foci of sarcoid tissue in the dermis after injection of Kveim antigen (× 75)

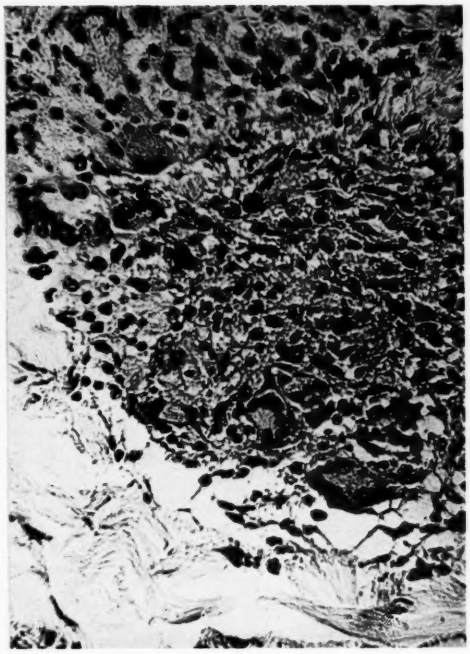

FIG. 2. Showing the epithelioid cells and giant cells in the sarcoid lesion after injection of Kveim antigen (×344)

FIG. 3. The reticulin stain reveals a fine network of reticulin fibrils passing through the sarcoid focus (× 344)

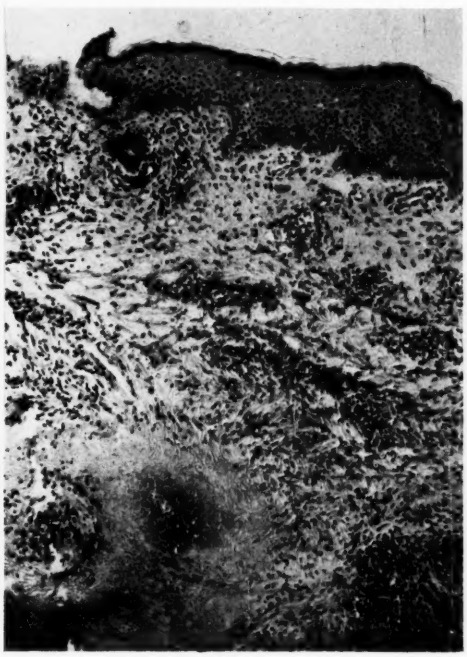

FIG. 4. Showing the necrotic type of reaction in the dermis after injection of Kveim antigen in a patient with active tuberculosis (× 75)

FIG. 5. Showing the necrotic area in the dermis in the tuberculous reaction (× 140)

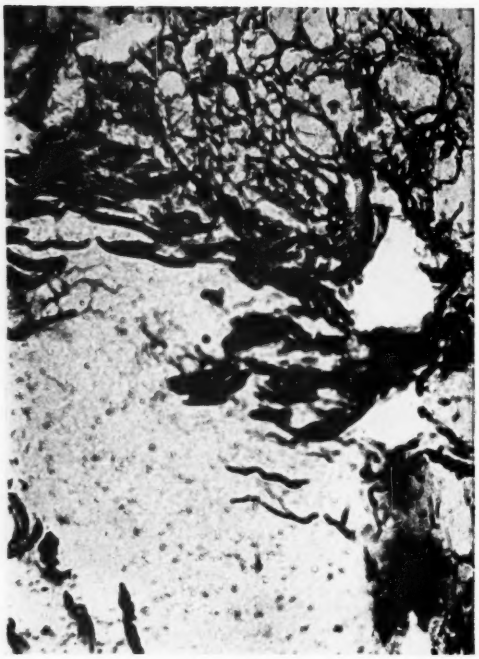

FIG. 6. Reticulin staining shows an absence of fibrils in the necrotic area (× 344)

FIG. 7. Showing a foreign-body giant-cell reaction in the dermis after injection of Kveim antigen (× 75)

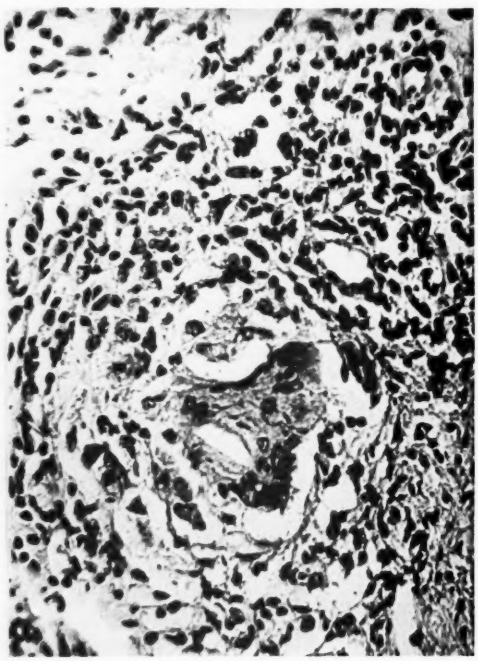

FIG. 8. Showing the foreign material in the cytoplasm of the giant cell, with a surrounding lymphocytic and polymorphonuclear cell response (× 344)

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TUBERCULOUS PLEURAL EFFUSIONS TREATED WITH STREPTOMYCIN, PARA-AMINOSALICYLIC ACID, AND EARLY ASPIRATION[1]

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After Waksman's discovery that streptomycin was active against the tubercle bacillus (Schatz, Bugie, and Waksman, 1944), it was realized that the organisms were liable to become resistant to the drug (Youmans, Williston, Feldman, and Hinshaw, 1946). After a course of streptomycin given as 1 gm. intramuscularly each day for 120 days, between 70 per cent. and 80 per cent. of the organisms tested were streptomycin-resistant (Medical Research Council, 1948*a*; Tucker, 1949; Warner, 1949; Tempel, Hughes, Mardis, Towbin, and Dye, 1950). In these circumstances there could be little justification for treating tuberculous pleural effusions with streptomycin, even though the drug was found to reach the pleural fluid in adequate concentrations (Zintel, Flippin, Nichols, Wiley, and Rhoads, 1945; Adcock and Hettig, 1946; Buggs, Pilling, Bronstein, and Hirshfeld, 1946; Steenken, d'Esopo, and Wolinsky, 1947). During 1949 several small series of patients with pleural effusions treated with systemic streptomycin were reported (Gerocarni, 1949; Chu, 1949; Moyer, 1949). Pfuetze and Pyle (1949) quoted no figures, but expressed the opinion that streptomycin reduced the duration of the toxaemia. They thought it reasonable to expect a lower incidence of recurrences and complications. No trials have yet been reported to support or disprove this hypothesis. Another approach to the problem was the introduction of streptomycin directly into the intrapleural space (Hinshaw and Feldman, 1945; Danopoulos and Melissinos, 1951). Other authors who advocated the use of intrapleural streptomycin in the treatment of pleural effusions have recommended that it should be combined with intramuscular streptomycin therapy (Nassi, 1948; Bracco, del Valle, and Howard, 1950). The disadvantage of these methods of treatment is the danger of producing streptomycin-resistant strains of tubercle bacilli. Various methods of delaying or preventing this occurrence have been developed. The combination of streptomycin with other antituberculous drugs delays the emergence of streptomycin-resistant organisms (Karlson, Pfuetze, Carr, Feldman, and Hinshaw, 1949; Dunner, Brown, and Wallace, 1949). When 20 gm. of *p*-aminosalicylic acid (PAS) and 1 gm. of streptomycin are given daily for 120 days, not more than 15 per cent. of streptomycin-resistant strains need be expected (Medical Research Council, 1952). Deyke, Fisher, James, and Sides (1949) first showed that an intermittent régime of streptomycin administration delayed the emergence of streptomycin-resistant organisms. Subsequent clinical trials confirmed the

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view that, when streptomycin was given as 1 gm. every third day for 120 days, only 30 per cent. to 40 per cent. of the organisms were likely to become streptomycin-resistant (Sides, 1949; Tucker, 1949; James, Sides, Dye, and Deyke, 1951). The combination of daily oral PAS with streptomycin injections given every third day further delays the emergence of streptomycin-resistant organisms (Mardis, 1949; Tempel, Hughes, Mardis, Towbin, and Dye, 1950). The infrequent emergence of resistant organisms with these improved régimes largely removes the objection to the streptomycin treatment of tuberculous pleural effusions.

The Present Investigation

In this section the results of treatment in a control group of 40 patients having tuberculous pleural effusions, treated with adequate rest in bed, are

TABLE I

Size of the Effusions in the Control and Streptomycin Groups

	Number	
Size of effusions	*Control group*	*Streptomycin group*
Very large . .	5	2
Large . . .	31	15
Moderate . .	5	8
Total . . .	41	25

compared with the results obtained in a group of 25 strictly comparable patients also treated with adequate rest, but in addition given a course of streptomycin and PAS. Nineteen of the 25 patients in the streptomycin group were also subjected to early therapeutic aspiration.

Description of cases

Sixty-five patients with tuberculous pleural effusions were treated. One of the control subjects had two effusions separated by a period of three months; both effusions are included in the study. Thus there are 40 patients and 41 effusions in the control group. All but four of the patients were Royal Air Force personnel in a R.A.F. Hospital. The four civilian patients were treated under exactly similar conditions.

Sex and age incidence. In the control group there were 36 male and 4 female patients. In the streptomycin group there were 19 male and 6 female patients. In view of the predominantly male Service population at risk, these figures in no way represent a true sex incidence. All the patients were between the ages of 18 and 25 years, except two (one in each group) aged 30 years.

The size of the effusions in the two groups is compared in Table I. Effusions less than moderate in size were not included in the study.

Criteria for diagnosis

Clinical features. Except in the four cases described below, there was in every instance an onset of pleurisy with effusion in an apparently healthy young adult.

There was no clinical evidence, such as a cough productive of purulent sputum, to suggest an underlying pneumonia or bronchiectasis as the cause of any of the effusions. In the streptomycin group two patients were already in hospital, resting in bed and receiving antibacterial therapy, when their effusions developed. One (S5) was being treated for a severe primary tuberculous pulmonary lesion, and the other (S18) for a minimal tuberculous lung lesion. In the control group, also, two patients were resting in bed in hospital at the time of the onset of their

TABLE II

Incidence of Lung Lesions seen on the Initial Radiographs

	Streptomycin group	*Control group*
Patients with lung lesions . . .	6 (at least two primary lesions)	8 (at least one primary lesion)
Patients with clear lung parenchyma .	19	32
Total	25	40

effusions. One (C30) was being treated for a primary tuberculous lung lesion, and the other (C39) for a minimal tuberculous lung lesion.

Radiographs. Every patient was radiographed on admission to hospital, and subsequently in accordance with clinical indications. In no circumstances was this done less frequently than once every four weeks while the patient was in hospital. After discharge radiographs were taken by the various chest physicians following up the patients, usually every three months for at least the first year, and thereafter at longer intervals. In all cases the radiographs were borrowed at intervals over the ensuing years, to assess the duration of pleural fluid or thickening and the incidence of subsequent pulmonary tuberculosis. The number of patients found to have parenchymal lung lesions, on the radiographs taken at the onset of their pleurisy, is shown in Table II. In all but one patient the lung lesions were minimal in extent. In this one patient (S17) there was infiltration and a medium-sized cavity in the left upper zone.

Mantoux tests. In every instance the Mantoux test was positive to first- or second-strength tuberculin P.P.D.

Pleural fluid. In every patient the presence of a pleural effusion was confirmed by the diagnostic aspiration of typical clear, straw-coloured fluid. In all cases the dominant cell was the lymphocyte. Of the 25 effusions in the streptomycin group, specimens of only two were injected into guinea-pigs, and both results were positive for tubercle bacilli. Cultures from the remaining 23 effusions were made on Löwenstein's medium, but only one grew tubercle bacilli. Of the 41 effusions in the control group, specimens of only seven were injected into guinea-pigs, and four gave positive results for tubercle bacilli. Cultures from the remaining 34 effusions were made on Löwenstein's medium, but only two grew tubercle bacilli.

Examination of sputum or gastric washings for tubercle bacilli. Three direct examinations and cultures of sputum or gastric washings were made for tubercle bacilli in all patients soon after admission, and at least once every month thereafter. A positive result was obtained in four of the 25 streptomycin group and in

nine of the 40 control group (Table III). In a further five patients in the streptomycin group tuberculous infiltration was present in the lung, without a positive result in the sputum or pleural fluid. Thus in 12 (48 per cent.) of the 25 streptomycin group there was definite evidence of tuberculosis. In a further four patients in the control group tuberculous infiltration was present in the lung, without a positive result in the sputum or pleural fluid, and in one other

TABLE III

The Frequency of Positive Results in Tests for Tubercle Bacilli

	Streptomycin group (25 patients)	*Control group (40 patients)*
Positive in pleural fluid .	3	6
Positive in sputum or gastric washing . .	4	9
Positive in pleural fluid, sputum, or gastric washing	7 (28%)	13 (32·5%)

the material removed at decortication showed histological evidence of tuberculosis. Thus in 18 (45 per cent.) of the 40 patients in the control group there was definite evidence of tuberculosis. It will be seen from the foregoing observations that the control and streptomycin groups were strictly comparable.

Description of treatment

Rest and antibacterial therapy. All the patients in both the streptomycin and control groups were kept strictly resting in bed for at least three months; after this, if there were no contra-indications, slowly increasing activity was allowed for a further three months. By the end of this time they were up all day and allowed to go for walks. All the patients in the streptomycin group were given a course of streptomycin sulphate and *p*-aminosalicylic acid (PAS). Fifteen to 20 gm. of PAS were given orally, in divided doses, every day for the duration of the streptomycin course. Various schedules of dosage were employed. The general principle followed was to give 1 gm. of streptomycin by intramuscular injection each day until the desired therapeutic response had been obtained, after which the injections were given once every third day. The total doses and régimes employed are given in Table VI (page 68). All the patients were treated only by rest in bed for at least seven days before antibacterial therapy was started, except the two who were already having antibacterial therapy at the onset of their effusions (S5 and S18). These periods of preliminary rest in fact varied between seven and 23 days. The longer delays were due to the fact that some of the patients were initially retained in other hospitals or wards before transfer to the author's care. The duration of the effusions, and of preliminary rest in bed, before starting antibacterial therapy, is shown in Table VI for each patient in the streptomycin group.

Aspiration. In every patient a small quantity of fluid was removed for initial diagnostic purposes. The indications for therapeutic aspiration were different in the two groups. In the control group therapeutic aspiration was carried out

early in seven patients because there was evidence of pressure, mediastinal displacement, or extension of the fluid over the apex of the lung, and in five patients when there had been no clearing of the fluid after five weeks' rest in bed. In one patient (C9) an operation for decortication of the lung was performed on the 180th day after the onset of the effusion. In the streptomycin group it was initially the practice to perform therapeutic aspiration as soon as possible after the start of antibacterial therapy. The fluid was removed as completely as possible, and 1 gm. of streptomycin sulphate in 10 ml. of sterile water instilled into the pleural space. It was hoped that the fluid would not recur. After treating 19 patients in this way the conclusion was reached that such therapy did not usually prevent the recurrence of the fluid after early aspiration in the pyrexial phase of the illness. This form of treatment was then abandoned, and the remaining six cases in the streptomycin group were treated without early therapeutic aspiration and intrapleural streptomycin.

Assessment of progress and response to treatment

The progress of the patients and their response to treatment were assessed by the following observations.

1. *Duration of pyrexia.* When Royal Air Force personnel develop pyrexia they are automatically admitted to sick quarters or hospital, where proper temperature records are kept. A record of the pyrexia from the onset of the effusion was available in every case. Thus the duration of the effusion and the pyrexia can be estimated in each case from the start of rest in bed. The total duration of pyrexia in each of the cases in the streptomycin and control groups is recorded in Tables VI and VII respectively (pages 68 and 69). In Table VI the duration of pyrexia before and after starting antibacterial therapy is also shown. An additional column shows the duration of the effusions before the start of antibacterial therapy. In the pyrexial sub-group, defined below, these times are the same as those defining the duration of pyrexia before antibacterial therapy was started.

Both the streptomycin and control groups are further subdivided into pyrexial and apyrexial sub-groups. The mean duration of pyrexia above 99° F. in these control and streptomycin pyrexial sub-groups will be compared. The control pyrexial sub-group comprises 30 patients (Cases C1 to C30) in whom the temperature was at or above 99·5° F. and showed no sign of settling during the first seven days of strict rest in bed. The mean duration of pyrexia above 99° F. in these cases, from the start of rest in bed, was 45 days. The streptomycin pyrexial sub-group comprises 18 patients (Cases S1 to S18) in whom the temperature was at or above 99·5° F. and showed no sign of settling during a period of at least seven days of rest in bed before the start of antibacterial therapy. Thirteen of these patients were subjected to early therapeutic aspiration. This practice was later abandoned when it became apparent that in these circumstances the fluid usually recurred. The mean duration of pyrexia above 99° F. in these cases, from the start of rest in bed, was 22 days. It is likely that this period would have been less, had there not been a mean delay of 10 days

before the start of antibacterial therapy. The mean duration of pyrexia after starting antibacterial therapy was 12 days. Table IV compares the mean duration of pyrexia in the control and streptomycin pyrexial sub-groups. The standard error of the difference between the two means is 10·9 days. The two means of 45 days and 22 days differ by more than twice the standard error of the difference. The difference may therefore be regarded as statistically significant. The probability is just over 20 to one against these results being due to chance.

TABLE IV

The Mean Duration of Pyrexia in the Control and Streptomycin Pyrexial Sub-groups

	Number of patients	*Mean duration of pyrexia (days)*		
		Before starting antibacterial therapy	*After starting antibacterial therapy*	*Total*
Control pyrexial sub-group . .	30	..	..	45
Streptomycin pyrexial sub-group.	18	10	12	22

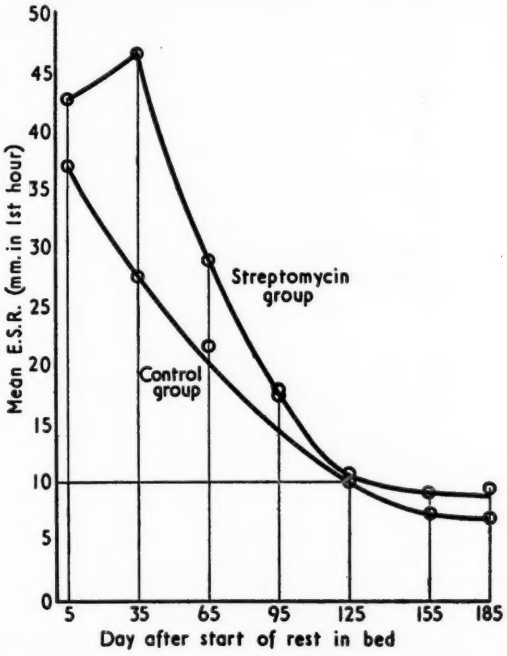
TABLE V

Comparison of the Means of the Erythrocyte Sedimentation Rates in the Control and Streptomycin Pyrexial Sub-groups on certain days after the Start of Rest in Bed

Day after starting rest in bed .	5	35	65	95	125	155	185
Mean E.S.R. (mm./hr.) (Control cases)	37	27·2	21·3	17·3	10·0	7·1	7·0
Mean E.S.R. (mm./hr.) (Streptomycin cases) . . .	42·5	46·5	28·8	17·2	10·1	9·3	9·6

2. *Duration of an accelerated erythrocyte sedimentation rate* (*E.S.R.*). In all cases E.S.R. readings were made on admission, and thereafter at least every four weeks. Westergren's method was used. For the purpose of this study 10 mm. in the first hour was arbitrarily regarded as the upper limit of normal in both sexes. The times taken for the initial E.S.R. readings to fall to 10 mm. or less in an hour are recorded in Tables VI and VII. The readings obtained in the control and streptomycin pyrexial sub-groups were compared as follows. Two large-scale graphs were compiled, one for each sub-group. Along the ordinates were plotted the E.S.R. readings, and along the abscissae the time, in days after the start of rest in bed, at which the readings were made. The points plotted for each case were joined by straight lines. From these two master graphs the estimated E.S.R. for all the cases in each sub-group, at any specific time after the start of rest in bed, could be read, and the mean E.S.R. for the sub-group at that time calculated. The times and results are recorded and compared in Table V. When these two sets of results are plotted on the same graph, the curves shown in the figure are obtained. It will be seen that in both the control and the streptomycin pyrexial sub-groups the mean E.S.R. fell below 10 mm. in an hour immediately after the 125th day. Antibacterial therapy and early therapeutic aspiration did not affect the duration of the accelerated E.S.R. in these cases. The curve relating to the control patients

shows a steady fall, whereas that relating to the streptomycin treated patients shows an initial rise to the 35th day, followed by a steady fall. The early therapeutic aspirations were performed between the fifth and 35th days, and undoubtedly account for this initial rise in the mean E.S.R. It was repeatedly noticed in individual cases that early aspiration was followed by a rise in the



Fall of the mean erythrocyte sedimentation rate to normal in the control and streptomycin pyrexial sub-groups.

E.S.R. Patients who were given antibacterial therapy without early therapeutic aspiration did not show this phenomenon. Danopoulos and Melissinos (1951) observed a similar rise in the E.S.R. after early aspiration and intrapleural streptomycin therapy without systemic streptomycin.

3. *Duration of the effusion.* The serial chest radiographs were studied, and an assessment made of the times from the start of rest in bed to the first radiographs which showed complete clearing of the fluid and no more than residual obliteration of the costophrenic angles. These times are shown in Tables VI and VII. It was possible to trace the eventual clearing of all the effusions, in both the control and the streptomycin groups, except in the one control patient (C9) whose lung was decorticated after 180 days. Clearing had still not taken place more than three years (more than 1,160 days) after the onset of his effusion. No conclusions can be drawn about the effect of antibacterial therapy on the clearing of the effusion. This is because the number of cases studied is small, the variation in the times of clearing great, and 13 of the 18 patients in the

TABLE VI

Progress of Patients in the Streptomycin Group

Case number	Lung fields on X-ray	Streptomycin régime (total gm. given)			Duration in days of raised erythrocyte sedimentation rate	Duration in days of effusion before starting S+PAS	Duration in days of temperature above 99° F.			Time from rest in bed to clearing of effusion on X-ray (days)	Progress of patients	
		Daily	Every third day	Total			Before starting S+PAS	After starting S+PAS	Total		Occurrence of further manifestations of tuberculosis	Most recent follow-up (months from onset)
S1	Clear	30	39	69	165	9	9	54	63	250		14 m.
S2	Clear	60	..	60	120	23	23	2	25	150		25 m.
S3	Clear	9	21	30	110	15	15	2	17	120		37 m.
S4	Clear	22	30	52	0	13	13	4	17	60		14 m.
S5	Lung lesion (primary)	(38)*+29 = 67	19	(38)+48 = 86	60	*	..	19	19	130		15 m.
S6	Lung lesion (primary)	19	11	30	120	10	10	15	25	150		24 m.
S7	Clear	18	12	30	165	7	7	13	20	150		24 m.
S8	Clear	4	26	30	175	11	11	1	12	90		25 m.
S9	Clear	4	26	30	40	8	8	2	10	30		27 m.
S10	Clear	17	13	30	20	11	11	2	13	80		24 m.
S11	Clear	11	39	50	75	8	8	10	18	180		24 m.
S12	Clear	7	23	30	105	16	16	10	26	140	Remaining well at	25 m.
S13	Clear	36	19	55	135	7	7	21	28	100		27 m.
S14	Clear	7	23	30	135	11	11	4	15	130		33 m.
S15	Clear	32	..	32	125	7	7	22	29	150		26 m.
S16	Lung lesion	22	10	32	95	13	13	20	33	90		23 m.
S17	Lung lesion	5	19	24	65	7	7	5	12	60		37 m.
S18	Lung lesion	(9)*+18 = 27	33	(9)+51 = 60	225+	*	..	13	13	90		24 m.
S19	Clear	4	26	30	35	9	No pyrexia	0	0	30		32 m.
S20	Clear	7	15	22	105	17	17	0	17	60		30 m.
S21	Clear	7	23	30	225	8	8	0	8	270		25 m.
S22	Clear	4	26	30	85	7	7	0	7	30		30 m.
S23	Clear	10	28	38	190	8	No pyrexia	0	0	190		26 m.
S24	Lung lesion	15	45	60	140	17	No pyrexia	0	0	190	Developed active pulmonary disease at 9 m. Well at	26 m.
S25	Clear	..	30	30	60	7	7	0	7	40	Remaining well at	28 m.

S+PAS = streptomycin and *p*-aminosalicylic acid.

* S+PAS given before onset of effusion.

streptomycin pyrexial sub-group were subjected to early therapeutic aspiration. It has not been the impression of any authors that antibacterial therapy reduces the duration of the effusion (Bauce and Vannini, 1951; Stadler, 1951).

4. *Incidence of subsequent tuberculosis.* After discharge from hospital all the patients were referred to the out-patient care of their local chest clinics. Letters were written to the various chest physicians requesting information about the

TABLE VII

Progress of Patients in the Control Group

Case number	Lung fields on X-ray	Duration in days of raised erythrocyte sedimentation rate	Duration in days of temperature above 99° F.	Time from rest in bed to clearing of effusion on X-ray (days)	Progress of the patients: Occurrence of further manifestations of tuberculosis	Most recent follow-up (months from onset)
C1	Clear	55	20	100	Developed active minimal pulmonary disease at 25 m. Well at	35 m.
C2	Clear	75	18	110	Developed active minimal pulmonary disease at 38 m. Well at	46 m.
C3	Clear	135	54	300	Remaining well at	27 m.
C4	Clear	155	17	180	Remaining well at	37 m.
C5	Clear	130	21	180	Remaining well at	28 m.
C6	Clear	130	35	900	Remaining well at	30 m.
C7	Clear	180	17	660	Developed active pulmonary disease at 12 m. Well at	60 m.
C8	Clear	50	14	120	Remaining well at	30 m.
C9		250	144	1,160+	Remaining well at	38 m.
C10	Clear	125	24	90	Remaining well at	24 m.
C11		370	300	340	Developed active pulmonary disease at 10 m. Well at	40 m.
C12	Clear	230	18	330	Remaining well at	49 m.
C13	Clear	120	66	690	Remaining well at	31 m.
C14	Clear	135	35	540	Developed active pulmonary disease at 29 m. Well at	47 m.
C15	Clear	210	32	60	Developed active pulmonary disease at 2 m. Well at	26 m.
C16	Clear	120	24	180	Remaining well at	28 m.
C17	Clear	135	20	30	Remaining well at	38 m.
C18	Clear	?	20	80	Remaining well at	46 m.
C19	Clear	165	40	630	Developed a contralateral effusion at 6 m. Well at	30 m.
C20	Clear	190	56	480	Developed T.B. cervical adenitis at 15 m. Well at	36 m.
C21	Clear	135	30	320	Remaining well at	38 m.
C22	Clear	60	130	80	Remaining well at	51 m.
C23	Clear	40	12	50	Remaining well at	30 m.
C24	Clear	165	43	70	Developed active pulmonary disease at 3 m. Well at	50 m.
C25	Clear	90	16	30	Remaining well at	30 m.
C26	Clear	115	20	120	Developed active pulmonary disease at 14 m. Well at	42 m.
C27	Lung lesion	80	47	140	Remaining well at	42 m.
C28	Lung lesion	90	33	330	Remaining well at	46 m.
C29	Lung lesion	95	15	50	Developed active pulmonary disease at 32 m. Well at	65 m.
C30	Lung lesion (primary)	145	9	230	Remaining well at	47 m.
C31	Clear	25	7	30	Developed ipsilateral effusion at 3 m. and active minimal pulmonary disease at 28 m. Well at	38 m.
C32	Clear	0	No pyrexia	1,200	Remaining well at	40 m.
C33	Clear	200+	5	210	Remaining well at	37 m.
C34	Clear	135	8	190	Remaining well at	24 m.
C35	Clear	185	10	470	Remaining well at	41 m.
C36	Clear	20	12	80	Developed a contralateral effusion at 12 m. Well at	42 m.
C37	Clear	45	5	20	Remaining well at	27 m.
C38	Lung lesion	200+	14	60	Remaining well at	27 m.
C39	Lung lesion	50	No pyrexia	130	Remaining well at	48 m.
C40	Lung lesion	50	13	50	Remaining well at	30 m.
C41	Lung lesion	60	16	120	Remaining well at	53 m.

patients' progress and the loan of the chest radiographs. All the patients remained under surveillance. The duration of the follow-up in each case is estimated as the time from the onset of the effusion and start of rest in bed to the most recent chest radiograph and examination by the chest physician. These times, in months, are recorded in Tables VI and VII, together with the progress and fate of the patients.

Of the 40 patients in the control group, all have been followed up for at least two years, 25 for at least three years, seven for four years, and two for five years. Further manifestations of tuberculosis had appeared in seven (17·5 per cent.) of the 40 patients by the end of the first year, and in nine (22·5 per cent.)

by the end of the second year. Of the 32 control subjects whose lung fields were initially clear, further manifestations of tuberculosis had appeared in seven (21·9 per cent.) by the end of the first year, and in nine (28·1 per cent.) by the end of the second year. Of the 25 patients in the streptomycin group, all have been followed up for at least one year, 21 for at least two years, and only two for three years. Of the 25 cases only one (4 per cent.) has broken down. This patient (S24) developed a local spread from a tuberculous lesion in the right upper lobe

TABLE VIII

Incidence of Further Manifestations of Tuberculosis in the First Two Years after Pleurisy with Effusion

	Control group cases			*Streptomycin group*		
	Number of patients followed for 2 years	*Patients developing further manifestations of tuberculosis in the first 2 years*		*Number of patients followed for 2 years*	*Patients developing further manifestations of tuberculosis in the first 2 years*	
		Number	%		*Number*	%
Patients with initially clear lung fields .	32	9	28·1	17	0	0
Patients with initial lung lesions . .	8	0	0	4	1	25
Total . . .	40	9	22·5	21	1	4·8

nine months after the onset of his pleurisy. This lesion had been present at the onset of the pleurisy. He was returned to rest in bed and given a further 50-day course of daily streptomycin and PAS. Fifteen months after the onset of the pleurisy the anterior segment of the right upper lobe and a wedge of the lateral border of the right lower lobe were resected. Convalescence was uneventful, and at the most recent follow-up, 26 months after the pleurisy, he was well and working. The chest radiograph showed that the remaining lung fields were clear. Thus further manifestations of tuberculosis had appeared in one (4·0 per cent.) of the 25 streptomycin patients followed up for at least one year, by the end of that first year, and in the same one (4·8 per cent.) of the 21 patients followed for at least two years, by the end of those first two years.

It is now possible to compare the follow-up results obtained in the control and streptomycin groups. A comparison of the two-year follow-up results gives the most useful information (Table VIII). In the first two years after their pleural effusions, subsequent manifestations of tuberculosis occurred in 22·5 per cent. of the 40 patients treated only by rest in bed, and in only 4·8 per cent. of the 21 patients treated with streptomycin and PAS. Eighteen of these 21 patients were subjected to early therapeutic aspiration. The standard error of the difference between these two percentages is 8·1. The difference between the two observed percentages, 22·5 and 4·8, is just over twice the standard error of the difference, and may be regarded as statistically significant. The probability is just over 20 to 1 against these results being due to chance. The results are even more striking when only patients who initially had clear lung fields are compared. In the first two years subsequent manifestations of tuberculosis occurred in 28·1 per cent. of the 32 patients treated only by rest in bed, but in none of the 17 patients treated with streptomycin and PAS. Fourteen of these

17 patients were subjected to early therapeutic aspiration. The standard error of the difference here is 8·0. The difference between the two observed percentages, 28·1 and 0, is three and a half times as great as the standard error of the difference; the probability is over 370 to one against these results being due to chance. The number of patients with initial lung lesions available for comparison is too small to be of statistical significance.

Discussion

In many ways the effect of antibacterial therapy in the early stages of tuberculous pleural effusions has been disappointing. The only positive advantage of such treatment in the early stages appears to be a shortening of the duration of pyrexia. This has been the impression of some previous authors who have described small numbers of cases (Chu, 1949; Gerocarni, 1949; Bauce and Vannini, 1951). The present study permits the conclusion that a significant reduction in the duration of the pyrexia is associated with the treatment of pleurisy with effusion by antibacterial therapy and early therapeutic aspiration. A very small minority of authors have suggested that early aspiration alone can reduce the duration of the pyrexia (Holmgren, 1911; Schottmüller, 1933), but this view has never been accepted generally, nor has its truth ever been demonstrated in a controlled series. In the present study it was not uncommon for the early aspirations to be followed by a rise in temperature, and there was invariably a rise of the erythrocyte sedimentation rate. For these reasons, and because the fluid tended to recur, early therapeutic aspiration as a routine measure was discontinued after the first 19 cases so treated. It is most probable that the shortening of the pyrexial period was due to the antibacterial therapy, and not to the early therapeutic aspirations. There was considerable variation in the response to treatment within the streptomycin group. Antibacterial therapy is by no means always effective in rapidly settling the temperature. Moyer (1949), who treated nine acute cases, reported a good initial response in only five. The uncertainty of this treatment is further emphasized by the fact that in two of the patients effusions and high pyrexia developed when they were already having streptomycin and PAS therapy, in one patient for a slight tuberculous lung lesion (S18), and in the other for a complicated primary tuberculous infection (S5). Other authors have had similar experiences (Trocmé, 1950; Bariéty and Lesobre, 1951).

The reasons for the variation in the response to antibacterial therapy are not known. One possible explanation is that those patients who fail to respond harbour streptomycin-resistant tubercle bacilli. Although such cases have been reported (Brennan and Wichelhausen, 1949; Arany and Lewis, 1950), they must be very uncommon; all the tubercle bacilli isolated from the 281 patients in the two Medical Research Council trials were sensitive to streptomycin before antibacterial therapy was started (Medical Research Council, 1950, 1952). The position with regard to patients who develop a pleural effusion during streptomycin therapy is a little different. In one of the two who did so in the present series (S18) the organisms had had little opportunity of becoming streptomycin-

resistant. Only 9 gm. of streptomycin had been given, with daily PAS, before the effusion appeared. In the other (S5) 38 gm. of streptomycin with daily PAS had been given before the effusion appeared. A streptomycin-resistant strain might have emerged, but it seems very unlikely. The alternative, and much more probable, explanation of the failure of streptomycin in some cases and not in others is to be found in the varying pathology and mode of occurrence of different effusions. It is not known to what extent the haematogenous dissemination of tubercle bacilli plays a part in the infection of the pleura and production of pleurisy with effusion. The haematogenous origin of pleural infection and effusion, when associated with extrapulmonary tuberculosis, has been reported by several authors (Jones and Dooley, 1946; Sibley, 1950). Bilateral effusions, even when they do not occur simultaneously, are believed to be due to the haematogenous dissemination of tubercle bacilli (Paine, 1941; Fernandes, 1944). Pagel (1943) observed instances of undoubted blood-borne pleurisy restricted to one side. Patients in whom tuberculous pleural effusions are due to haematogenous infection are those who might be expected to benefit most from antibacterial therapy.

A study of the literature shows that the treatment of pleurisy with effusion by prolonged rest in bed does not prevent about 30 per cent. of patients from subsequently developing active tuberculosis (Emerson, 1954). The follow-up of the present control group shows a similar high incidence. It may be concluded from the present study that the treatment of pleurisy with effusion by antibacterial therapy and early therapeutic aspiration resulted in a lowered incidence of active tuberculosis in at least the first two years after the pleurisy. Some authors have suggested, on theoretical grounds, that early therapeutic aspiration alone might lower the incidence of subsequent tuberculosis, by reducing the duration of the pleural fluid and residual thickening (Uehlinger, 1946). No such effect has ever been demonstrated in a controlled trial. In the present study the fluid usually recurred after early therapeutic aspiration, done during the pyrexial phase of the illness, and such aspiration was abandoned for this reason. It is probable that the lower incidence of subsequent tuberculosis was due to the antibacterial therapy. In the 40 control subjects three further pleural effusions (two contralateral) and one case of tuberculous cervical adenitis occurred in the first two years. Such lesions would be expected to occur as a result of the haematogenous dissemination of tubercle bacilli. On theoretical grounds they are the lesions most likely to be prevented by antibacterial therapy. No such non-pulmonary lesions occurred in the patients who were given antibacterial therapy. It is gratifying that not one of the 17 patients of the streptomycin group who initially had clear lung fields developed any further manifestation of tuberculosis in the two-year follow-up period. Antibacterial therapy is not always as effective as in the present series, and does not necessarily prevent subsequent tuberculosis. Bariéty and Lesobre (1951) reported two cases of pulmonary tuberculosis occurring some months after pleural effusions treated with streptomycin.

It remains to consider the indications for starting antibacterial therapy in

cases of tuberculous pleurisy with effusion. Current teaching, as reflected in modern textbooks, certainly does not advise that it should be given to all patients (Pagel, Simmonds, and Macdonald, 1953; Robson, 1952; Young, 1952). The only objection that has been raised is the danger of developing streptomycin-resistant tubercle bacilli (Crofton, 1952). There is no information available as to how often streptomycin-resistant organisms can be isolated from tuberculous patients who have had a tuberculous pleural effusion treated with streptomycin. Any assessment of the likelihood of such streptomycin-resistant strains emerging must be made from the available observations on cases of miliary, meningeal, and pulmonary tuberculosis treated with streptomycin. There is a parallel between some cases of pleurisy with effusion, due to the haematogenous dissemination of tubercle bacilli, and miliary tuberculosis. In the early Medical Research Council trials streptomycin-resistant organisms were encountered in only three of 22 cases of miliary tuberculosis, although the patients were treated with daily streptomycin without PAS (Medical Research Council, 1948*b*). The emergence of streptomycin-resistant strains has been extensively studied in cases of open pulmonary tuberculosis. The infrequency with which streptomycin-resistant strains emerge after régimes of intermittent streptomycin combined with PAS is most encouraging (Tempel, Hughes, Mardis, Towbin, and Dye, 1950), and especially so when the following points are remembered. The 95 patients studied by Tempel and his colleagues all had moderately or far advanced pulmonary tuberculosis, and in 83 of them there was definite cavitation. Such cases are always used in resistance studies, because they are those from which tubercle bacilli are most likely to be available for study before and after the course of antibacterial therapy. They are, however, the very cases most likely to develop streptomycin-resistant organisms. This fact has been demonstrated by authors who have compared the number of streptomycin-resistant organisms obtained from groups of patients with and without persistent cavitation after streptomycin therapy (Mitchell, 1949; Howlett, O'Connor, Sadusk, Swift, and Beardsley, 1949; Howard, Maresh, Mueller, Yannitelli, and Woodruff, 1949; James, Sides, Dye, and Deyke, 1951). It is also probable that streptomycin-resistant organisms emerge more readily in patients who are clinically ill when starting streptomycin, or whose chest radiographs show confluent disease shadows (Bignall, Clegg, Crofton, Smith, Holt, Mitchison, and Armitage, 1950). Patients contracting pleurisy with effusion, unless it is secondary to established pulmonary tuberculosis, have neither intrapulmonary cavities nor confluent disease shadows. The likelihood of streptomycin-resistant organisms emerging as a result of the treatment of pleural effusions with intermittent streptomycin and daily PAS must be very small. Against the slight risk of developing streptomycin-resistance is to be set the advantage of shortening the duration of the pyrexia and the period of discomfort for the patient, and considerably decreasing his chances of developing subsequent active tuberculosis. It is recommended that all patients who have tuberculous pleurisy with effusion, irrespective of the degree or duration of the pyrexia, should be given the benefit of antibacterial therapy.

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Summary

Forty young adults with tuberculous pleural effusions were treated by adequate rest in bed, and the results are compared with those obtained in a group of 25 strictly comparable patients, also treated with adequate rest in bed, but in addition given a course of streptomycin and PAS. Nineteen of these 25 patients were also subjected to early therapeutic aspiration.

The mean duration of pyrexia in the streptomycin group was 22 days, compared with 45 days in the control group. This difference is statistically significant.

There was no difference in the duration of the raised erythrocyte sedimentation rate in the two groups. No conclusions can be drawn about the effect of the treatment on the duration of the effusion.

Of the patients who were followed up for at least two years, active tuberculosis developed in nine (22·5 per cent.) out of 40 in the control group, but in only one (4·8 per cent.) out of 21 in the streptomycin group. Of the patients followed up for at least two years in whom the lung parenchyma was initially clear, active tuberculosis developed in nine (28·1 per cent.) out of 32 in the control group, but in none of the 17 in the streptomycin group. These differences are statistically significant.

It was initially the practice to carry out early therapeutic aspiration in the patients who were given antibacterial therapy. This practice was discontinued after 19 cases because, after such early therapeutic aspiration in the pyrexial phase of the illness, the fluid usually recurred, the erythrocyte sedimentation rate was invariably accelerated, and the temperature sometimes increased. It is argued that the shortening of the pyrexial period and the lowered incidence of subsequent tuberculosis in the streptomycin group are due to the antibacterial therapy, and not to the early therapeutic aspirations.

It is recommended that all patients with a tuberculous pleural effusion should be given the benefit of antibacterial therapy.

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THE CLINICAL INVESTIGATION OF THE PORTAL CIRCULATION, WITH SPECIAL REFERENCE TO PORTAL VENOGRAPHY[1]

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With Plates 7 and 8

Only in recent years has it become possible to demonstrate the portal venous system radiographically (Table I). The introduction of the portocaval shunt operation provided an opportunity whereby radio-opaque material could be introduced into the portal vein. Portal venography in man was first recorded in 1947 by Fariñas, who injected contrast medium into the long saphenous vein of a patient who had a portocaval anastomosis, thus outlining the portal vein and its intrahepatic branches. Dotter, Payne, and O'Sullivan (1950) passed a cardiac catheter along the inferior vena cava and through the portocaval anastomosis, and injected the contrast medium directly into the portal vein. Portal venography performed at laparotomy was described by Blakemore and Lord (1945), and has since been reported by de Sousa Pereira (1949), Child, O'Sullivan, Payne, and McClure (1951), Leger, Gally, Arvay, Oudot, and Auvert (1951), and Moore and Bridenbaugh (1951). Child and his colleagues reported 14 portal venograms made by injecting contrast medium into a tributary of the superior mesenteric vein. They were able to demonstrate displacement and occlusion of the portal vein in local malignant and inflammatory conditions, and to outline collateral channels in such cases. The size of the liver could be determined from the distribution and size of the intrahepatic portal branches. Celis, Espinosa, and Fregoso (1948) outlined the portal vein by means of contrast medium injected through a catheter inserted into the superficial collateral channel on the anterior abdominal wall in a patient who had a persistent umbilical vein (Cruveilhier-Baumgarten syndrome). Abdominal-wall collaterals, however, are very seldom large enough for the portal vein to be outlined by this means. Steinbach, Bierman, Miller, and Wass (1953) passed a needle through the anterior abdominal wall into an intrahepatic branch of the portal vein, injected diodrast, and so outlined the intrahepatic branches of the portal system. This procedure, which is not without risk to the patient, does not give information about the extrahepatic portal bed. Rigler, Olfelt, and Krumbach (1953) performed splanchnic arteriography by injecting contrast medium into the

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aorta at the level of the 10th thoracic vertebra. Eight seconds after the completion of the injection the contrast medium had passed through the splanchnic bed, clearly outlining the splenic and portal veins.

The discovery that contrast medium injected into the pulp of the spleen enters the portal blood-stream with sufficient rapidity to outline the splenic and portal veins was made by Abeatici and Campi (1951). They injected 6 to 9 ml. of

TABLE I

Methods for the Radiographic Demonstration of the Portal Venous System in Man

Method	*Date*	*Authors*	*Number of patients*
Via saphenous vein and inferior vena cava in patients with porto-caval anastomosis	1947	Fariñas	1
	1950	Dotter, Payne, and O'Sullivan	1
Via collateral channel in abdominal wall	1948	Celis, Espinosa, and Fregoso	1
Via portal vein tributary at operation	1945	Blakemore and Lord	15
	1949	de Sousa Peireira	..
	1951	Moore and Bridenbaugh	..
	1951	Child, O'Sullivan, Payne, and McClure	14
	1951	Santy and Marion	15
	1951	Leger, Gally, Arvay, Oudot, and Auvert	..
Percutaneous trans-hepatic route	1953	Steinbach, Bierman, Miller, and Wass	10
Following splanchnic arteriography	1953	Rigler, Olfelt, and Krumbach	..
Trans-splenic route: at operation	1951	Leger	1
percutaneous	1951	Boulvin, Chevalier, Gallus, and Nagel	2
	1952	Campi and Abeatici	14
	1952	de Scoville and Leroux	1
	1952	Dreyer and Budtz-Olsen	10
	1952	Sotgiu, Cacciari, and Frassineti	4
	1953	Walker, Middlemiss, and Nanson	12
	1953	Bahnson, Sloan, and Blalock	6
	1953	Morrow	24
	1953	Konar and Sen Gupta	14
	1953	Cooper, Brown, Stone, and Ferguson	12
	1953	Dantos, Rocha, and Barros Filho	20
	1953	Gvozdanović, Hauptmann, Najman, and Oberhofer	17
	1953	Rousselot, Ruzicka, and Doehner	5
	1953	Leger, Proux, and Arnavielhe	2
	1954	Fuld and Irwin	50
	1954	Dreyer	15
	1954	Dogliotti and Abeatici Dogliotti, Abeatici, and Campi	84
	1954	Caroli and Porcher	60

70 per cent. diodone rapidly into the spleen of dogs, films being taken at intervals up to one minute after the completion of the injection. The splenic and portal veins were best outlined at three to four seconds, and by 15 seconds only a residue remained in the splenic pulp. Leger (1951) performed trans-splenic portal venography at laparotomy by injecting 12 ml. of 70 per cent. diodone into the spleen, without ill effects. In the same year Boulvin, Chevalier, Gallus, and Nagel recorded for the first time the percutaneous injection of contrast medium

directly into the spleen, so obtaining a portal venogram. Dreyer and Budtz-Olsen (1952) suggested that percutaneous trans-splenic portal venography was useful in the demonstration of the intrahepatic portal circulation, in the diagnosis and localization of extrahepatic obstructions of the portal vein, and in the demonstration, after operation, of a patent portocaval anastomosis. This technique has since been used as a measure preliminary to portocaval anastomosis, to determine the patency of the splenic and portal veins, and to decide on the operative approach (Walker, Middlemiss, and Nanson, 1953; Bahnson, Sloan, and Blalock, 1953). Leger, Proux, and Arnavielhe (1953) detected metastases in the liver by means of trans-splenic portal venography, and mentioned the possible use of the method to avoid laparotomy in patients who have intra-abdominal neoplasms with liver metastases. Trans-splenic portal venography has been recommended as a measure preceding operation on patients with carcinoma of the pancreas, to demonstrate involvement of the splenic or portal vein (Cooper, Brown, Stone, and Ferguson, 1953). In the present paper an attempt has been made to evaluate the indications for the diagnostic use of trans-splenic portal venography, and to compare it with other clinical methods available for the demonstration of portal-systemic collateral channels.

Patients Investigated

A satisfactory portal venogram was obtained in 35 of the 40 patients investigated. Of these 35 patients 21 suffered from portal cirrhosis, and one of these had a portocaval anastomosis. Biliary cirrhosis was present in seven patients; in four it was of the primary type, and in three secondary to traumatic stricture of the bile-duct. In two patients an extrahepatic obstruction of the portal or splenic vein was suspected. The five patients of the miscellaneous group with suspected portal hypertension were suffering from sarcoidosis (Case 34), subacute hepatitis (Case 31), haemochromatosis (Case 32), idiopathic splenomegaly (Case 33), and fatty liver (Case 35).

Methods

Portal venography was performed only on patients who had a normal plasma prothrombin and blood-platelet count. After premedication with morphia gr. $\frac{1}{4}$, the patient was placed on a Schonander biplane serial angiographic table, and control films, including the lower thorax and upper abdomen, were taken in the anteroposterior and lateral projections. The following radiographic factors were used: anteroposterior: 400 mA., 0·06 second at 85 kV.; lateral: 400 mA., 0·08 to 0·09 second at 90 kV. In adults local anaesthesia was used, but children required general anaesthesia with nitrous oxide, oxygen, trilene, and short-acting relaxants. A fine lumbar-puncture needle (0·75 mm. outside diameter and 7 cm. in length), fitted with a stilette, was inserted through the eighth or ninth intercostal space in the mid-axillary line, directing the tip at an angle of 45° to the transverse plane. When the spleen was reached a resistance could be felt, and thereafter the patient was asked to take shallow breaths, or in the case of general anaesthesia apnoea was induced. After penetrating 2 cm. into

the spleen the stilette was removed, and blood could be seen to drip from the needle. This was a most valuable indication that the needle was in the spleen, and the injection was not made until it was seen. The swing of the needle with respiration was not in any way impeded, and while the tubing was being attached to the needle the patient was asked to hold his breath. The intrasplenic pressure was measured (Atkinson and Sherlock, 1954), and the needle was then connected to a 100 ml. syringe by a polythene tube of 2 mm. outside diameter using screw adaptors which ensured a firm union both to the needle and to the syringe. Fifty ml. of 50 per cent. diodone were injected by manual pressure, using a lever attached to the piston of the syringe. The time taken for the injection varied between seven and 10 seconds. Ten films were exposed in the anteroposterior and 10 in the lateral plane at a rate of one per second. The interval between the beginning of the injection and the first film, usually one to two seconds, was measured by stop-watch. Flushing of the skin, followed by a peculiar taste coming on within 30 seconds of the injection, was a good indication that the contrast medium had been injected into the spleen rather than into the peritoneal cavity. An hourly pulse chart was kept for 12 hours after the patient's return to the ward.

Barium studies of the oesophagus, using a standard procedure with thick and thin barium paste, the Valsalva manœuvre to distend the varices, and examinations in the erect and supine positions, were carried out on all patients. Oesophagoscopy with a flexible instrument was performed in 26 patients. Occluded hepatic vein pressure was measured by catheterization of the hepatic vein. It has been shown that this pressure approximates to the portal venous pressure (Paton, Reynolds, and Sherlock, 1953).

Results

Portal venography has been performed successfully in 35 out of the 40 patients in whom it has been attempted (Table II). In eight patients the injection was made into the peritoneal cavity, but in three of these the examination was repeated later with success.

After-effects. No serious after-effects have been encountered, and pain resulted only when the contrast medium was injected into the peritoneal cavity. Pain was due to peritoneal irritation, and was felt locally and in the left shoulder. In no case did severe pain last for more than an hour. Clinical signs of haemorrhage from the spleen were not encountered in any of our patients. The spleens of seven patients have been examined at autopsy or after splenectomy, 10 days to six months after portal venography. The site of injection could be identified as an intrasplenic haematoma in the one spleen examined 10 days after injection. In the other six there was no visible abnormality.

For descriptive purposes results have been classified according to radiographic appearances rather than clinical findings, as similar pictures may be produced by different pathological processes, and in the same disease appearances may vary with the degree of portal obstruction. The radiographic findings are described under three headings, namely those considered to be normal,

TABLE II

Findings in 35 Patients subjected to Portal Venography

	Portal cirrhosis																Biliary cirrhosis						Portal or splenic vein occlusion							Porto-caval anasto-mosis	Miscellaneous group				
Case number	1	2	3	4	5	6	7	8	9	10	11‡	12	13	14	15	16	17	18	19	20‡	21	22	23	24	25*	26*	27*	28†	29*	30*	31	32	33	34	35
Veins demonstrated by portal venography:																																			
Splenic vein	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	o	+	o	+	+	+	+	+	+	+	+	+
Portal vein	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	o	o	o	o	o	+	+	+	+	+	+	+
Left gastric and gastric varices	+	+	+	+	+	+	+	+	+	+	+	o	+	o	+	+	+	+	+	o	o	o	+	+	+	+	+	+	+	o	o	o	o	o	o
Oesophageal	+	+	+	+	+	+	+	+	+	+	o	+	+	o	+	+	+	+	+	o	o	o	+	+	+	+	+	o	+	o	o	o	o	o	o
Inferior mesenteric	+	o	+	+	+	o	o	o	o	o	o	o	o	o	+	o	+	o	o	o	o	o	+	o	o	+	+	o	+	o	o	o	o	o	o
Anterior abdominal wall	o	o	o	+	o	o	o	o	o	o	+	o	+	o	o	o	o	o	o	o	o	o	o	+	o	o	o	o	o	o	o	o	o	o	o
Spleen-diaphragm	o	o	o	+	+	o	o	o	+	+	o	o	o	o	o	o	o	+	o	o	o	o	+	+	+	+	o	o	+	o	o	o	o	o	o
Liver-diaphragm	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	+	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Lumbar	o	o	o	o	o	o	o	o	+	o	o	o	o	o	o	o	o	o	o	o	o	o	+	+	o	+	+	+	+	o	o	o	o	o	o
Inferior vena cava	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	+	o	o	o	o	o	+	o	o	o	o	o
Abnormality of liver pattern	o	+	+	o	o	+	+	+	o	o	+	+	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Previous gastro-intestinal bleeding	+	+	+	+	+	+	+	o	o	+	+	+	o	o	+	o	o	o	+	+	o	o	+	+	o	o	o	o	+	+	o	o	o	o	o
Varices seen on oesophagoscopy	+	+	..	+	+	+	+	+	o	o	o	+	+	o	+	o	..	..	+	o	o	o	+	+	+	..	..	o	+	(+)	..	o	..	..	..
Varices seen on barium swallow	+	o	+	+	+	+	+	+	o	o	o	+	+	o	+	+	o	o	o	o	o	o	o	o	+	o	+	o	+	o	o	o	o	o	o
Spleen-liver time (seconds)	..	..	..	..	..	6	3	5	5	4	3	..	4	2	4	3	..	4	5	..	..	2	..	..	..	..	..	..	..	o	2	..	2	2	..
Occluded hepatic vein pressure (mm. Hg) (normal 2–12)	..	..	33	21	21	..	18	20	20	..	22	..	..	6	..	..	21	..	14	..	20	18	12	..	7	10	10	6	6	o	..	10	15	9	..
Splenic pressure (mm. Hg) (normal 3–17)	40	24	35	25	25	..	34	22	24	..	29	..	28	19	30	27	27	..	17	..	28	22	29	..	25	20	25	24	18	18	3	17	21	9	12

* Patient had also portal cirrhosis. † Patient had also biliary cirrhosis. ‡ Patient had also peptic ulcer. (+) Varices were collapsed.

those showing intrahepatic portal venous obstruction, and those showing obstruction of the main portal vein or splenic vein.

Normal appearances. In the normal portal venogram (Plate 7, Fig. 2) all the contrast medium passed through the liver, and only the splenic vein and the portal vein with its intrahepatic branches were outlined. From the pool in the spleen contrast medium passed into hilar veins, which joined to form the splenic vein. This vessel ran a tortuous course to unite in front of the first lumbar vertebra with the superior mesenteric vein, the proximal portion of which was sometimes made visible by reflux of contrast medium. A clear area was occasionally seen in the portal vein where the superior mesenteric vein joins it. Most of the contrast medium entered the right lobe of the liver. The branches in the left lobe were less well filled, and in some cases were not visible. The intrahepatic portal branches ran a straight course, and showed a regular diminution in size with each successive division. The hepatic veins could not be identified. Occasionally leakage of contrast medium around the spleen outlined that organ, giving some indication of its size and shape.

Intrahepatic portal venous obstruction. In this group a proportion of the contrast medium passes into collateral channels and by-passes the liver (Plate 7, Fig. 3). The left gastric vein, filling from either the splenic or the portal vein and joining the gastro-oesophageal or para-oesophageal veins, was the collateral most frequently demonstrated (Table II). Radiologically no differentiation could be made between the intramural and para-oesophageal collaterals. Veins were sometimes seen running from the spleen to the diaphragm and abdominal wall. In one patient veins passed through the liver capsule to the right diaphragmatic dome, and were presumably the veins of Sappey passing through the bare area of the liver. Occasionally contrast material was seen to enter the inferior mesenteric vein from the splenic vein. In lateral radiographs other veins were seen running to the anterior abdominal wall (Plate 7, Fig. 4). These represented collaterals passing from the left branch of the portal vein in the falciform ligament, at the site of the obliterated umbilical vein. In all patients, although a considerable amount of blood was diverted through collaterals, sufficient contrast medium reached the liver to outline the intrahepatic branches. The intrahepatic portal vessels often showed tortuosity, irregularity of branching, and pooling of the contrast medium. A large branch of the portal vein would give off narrow branches, and the normal proportional reduction in size from the hilum to the periphery was lost. These intrahepatic changes were seen only in patients who showed a collateral circulation, and even then were not constant.

Extrahepatic obstruction of the portal or splenic vein. In this group the radiological appearances varied according to the site and degree of obstruction. Two patients (Cases 25 and 27) showed complete occlusion of the portal vein, and in three (Cases 24, 26, and 28) the splenic vein was completely obstructed. Partial occlusion of the portal vein was demonstrated in two patients (Cases 23 and 29). The striking feature of these cases was the massiveness of the collateral channels proximal to the obstruction, increasing with the degree of obstruction (Plate 8,

Fig. 5). The three cases of obstruction in the portal vein showed filling of a very large left gastric vein, and a striking conglomeration of oesophageal collaterals. In the three patients with splenic vein thrombosis the lumbar veins were clearly defined in the lateral film. They communicated through the long lumbar veins with the hemiazygos, or through the left suprarenal or renal vein with the inferior vena cava. There were two instances of partial obstruction of the portal vein, in one case at the junction with the superior mesenteric vein and in the other in the porta hepatis. Filling of the major intrahepatic branches was delayed, and no detailed vascular pattern was seen. The site of obstruction was shown by a filling defect. This defect must be distinguished from the 'dilution streaming' effect produced by reflux from the superior mesenteric vein.

Two patients of particular interest will be described in detail:

Case 23. A boy who had multiple liver abscesses, resulting from appendicitis, at the age of 13 years, was seen four years later on account of gastrointestinal bleeding. Splenomegaly was the only abnormal clinical finding. Serum biochemistry gave no evidence of liver-cell damage, and aspiration biopsy of the liver showed normal histological appearances. Oesophageal varices were not seen on examination by barium swallow, but were found on oesophagoscopy. The portal venogram (Plate 8, Fig. 6) showed an extensive collateral circulation, involving the left gastric and para-oesophageal veins and inferior mesenteric veins. Several collaterals extended from the spleen to the diaphragm, and further collaterals could be seen in the lateral view, ascending to the anterior chest wall and passing to the lumbar region. The intrahepatic portal tree presented a mottled appearance at the hilum, and some tortuous portal radicals reached the lower part of the right lobe. It seemed probable that scar tissue was constricting the portal vein as it entered the liver and grossly distorting the major intrahepatic branches.

Case 24. A girl of 11 years was seen on account of gastrointestinal bleeding. Splenomegaly was the only clinical abnormality, and serum biochemistry and aspiration biopsy showed no evidence of liver disease. No varices were seen on examination by barium swallow, but varices were found on oesophagoscopy. The portal venogram in the anteroposterior view (Plate 8, Fig. 7*a*) showed two large tortuous veins arising from the spleen; in the lateral view (Plate 8, Fig. 7*b*) these veins were seen to communicate posteriorly with the lumbar veins. Contrast medium entered the inferior vena cava from a vein at the level of the first lumbar vertebra, presumably the left renal vein. Collaterals also passed through the splenic capsule to reach the diaphragm and the lateral chest wall. The splenic and portal veins did not fill, and no contrast medium reached the liver. These changes were considered to be due to the occlusion of the splenic vein from an unknown cause, with a collateral circulation through the lumbar and left renal veins to the inferior vena cava.

Portocaval anastomosis. Portal venography has been used to demonstrate the patency of a portocaval anastomosis in one patient.

Case 30. A moulder, aged 42 years, with portal cirrhosis, had had an end-to-side portocaval anastomosis two years previously, after recurrent gastrointestinal bleeding. He had no further bleeding after the operation, but one year later developed episodes of mental confusion and a hepatic 'flapping' tremor. Splenomegaly was present, but no collateral channels were visible on the

abdominal wall, and barium swallow examination showed no evidence of varices. Oesophagoscopy revealed a few collapsed varices. At portal venography only the splenic vein, the proximal part of the portal vein, and the inferior vena cava were outlined, confirming the patency of the portocaval anastomosis and demonstrating that a collateral circulation was no longer present.

The portal venogram in portal and biliary cirrhosis. (1) *Portal cirrhosis.* Twenty of the 21 patients who were studied had gastrointestinal bleeding or

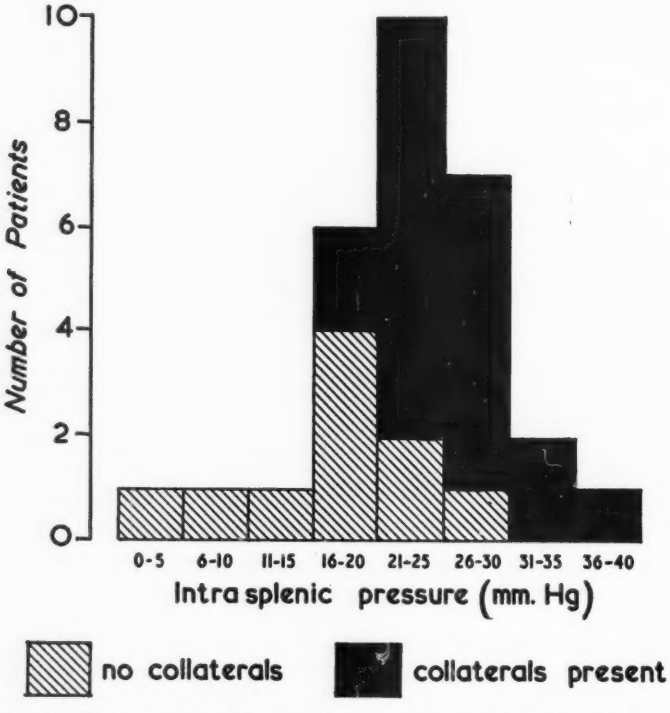

FIG. 1. Histogram showing that the presence of a collateral circulation is related to the degree of portal hypertension, of which the intrasplenic pressure is used as an index.

ascites, or both, with splenomegaly, which clinically suggested portal hypertension. Fifteen of these patients showed evidence of intrahepatic obstruction in the portal venogram. In four patients the portal venogram showed that the cirrhosis was complicated by portal or splenic vein thrombosis, which had not been suspected previously. One patient had had a previous portocaval anastomosis. In the 21st patient there were no symptoms or signs of portal hypertension, and the portal venogram was normal. (2) *Biliary cirrhosis.* Three of the seven patients showed normal portal venographic appearances, three showed venographic evidence of intrahepatic obstruction, and the seventh had a clinically unsuspected thrombosis of the splenic vein. None of these patients had symptoms of portal hypertension at the time of venography. One patient with

intrahepatic portal obstruction later had a gastrointestinal haemorrhage, and the value of the preceding portal venograph was demonstrated.

Case 19. A tailor, aged 60 years, had a bile-duct stricture, which followed cholecystectomy five years previously. There was slight jaundice, with hepatomegaly and splenomegaly, but no ascites. Barium swallow examination did not demonstrate varices. The portal venogram showed collateral channels in the region of the left gastric and para-oesophageal veins. Melaena occurred while he was awaiting operation for relief of his bile-duct stricture. The possibilities of hypoprothrombinaemia and duodenal ulcer associated with biliary obstruction were considered, but in view of the abnormal portal venogram his gastrointestinal bleeding could be attributed to ruptured oesophageal varices. This diagnosis was later confirmed by autopsy.

The relative value of portal venography, examination by barium swallow, and oesophagoscopy. Barium swallow examination failed to reveal oesophageal varices in nine (39 per cent.) of the 23 patients in whom they were outlined at portal venography. Varices were seen at oesophagoscopy in 15 of the 18 patients in whom oesophageal collaterals were demonstrated by portal venography. In no patient were varices detected by barium swallow or oesophagoscopy where portal venography had failed to reveal them (Table II). Portal venography therefore demonstrated a greater proportion of oesophageal varices than examination by barium swallow or oesophagoscopy, alone or in combination.

The collateral circulation in relation to the portal venous pressure. In general there was a good correlation between the height of the intrasplenic pressure, when used as an index of portal venous pressure, and the presence of a collateral circulation (Fig. 1). Portal hypertension was present in every patient in whom collateral channels had developed, although several had a raised portal pressure without demonstrable collaterals. In the group of patients with portal cirrhosis the extent of the collateral circulation was roughly proportional to the degree of portal hypertension, as measured either by hepatic vein occlusion or from the intrasplenic pressure. This was not so in the group of patients with biliary cirrhosis, of whom two had a raised portal venous pressure and yet showed a normal portal venogram. In the case of obstruction of the main portal or splenic vein, only the intrasplenic pressure can be used as an index of the venous pressure proximal to the block. This measurement correlated with the extent of the collateral circulation.

Speed of flow in the portal vein. The time from the commencement of the injection to the appearance of contrast medium in the smaller intrahepatic branches was found to be two seconds in each of five patients who showed a normal portal venogram. Three of these patients had evidence of an increased portal venous pressure. Each of 11 patients who showed venographic evidence of intrahepatic portal obstruction had a prolonged spleen-liver circulation time (three to six seconds). Thus portal venous stasis was present only after collateral channels had developed, and did not occur with portal hypertension alone.

Discussion

Percutaneous trans-splenic portal venography has become a recognized procedure in the clinical investigation of portal hypertension. Its use has been recorded in more than 350 patients without fatality (Table I). In the present series there were no fatalities or major complications, and with careful technique and selection of patients it should be free of serious risk if carried out in a well-equipped hospital. Walker, Middlemiss, and Nanson (1953) reported haemorrhage occurring two days after trans-splenic venography. At operation a tear was seen in the splenic capsule, and splenectomy was performed. Trans-splenic venography is advisable before surgical operations are undertaken on the portal venous system, and the venograph obtained determines both the nature and the practicability of the operation. Thrombosis of the splenic or portal vein, for instance, precludes anastomotic operations with the systemic circulation, and direct surgical attack on the oesophageal varices may be indicated. If the spleen has not been removed, the method provides the only certain means of demonstrating the patency of the portocaval anastomosis (Walker, Middlemiss, and Nanson, 1953; Jahnke, Palmer, Sborov, Hughes, and Seeley, 1953). Trans-splenic venography may be used in the diagnosis of the source of gastrointestinal haemorrhage in patients with splenomegaly. The demonstration of an extensive collateral circulation suggests that the bleeding has been from oesophageal or gastric varices, as in Case 19. Portal venography may be of some value in prognosis. The outlook for the patient with portal cirrhosis is much better if there is no portal collateral circulation, and therefore no risk of gastrointestinal bleeding. In patients with portal hypertension the prognosis varies with the cause. If due to hepatic cirrhosis, gastrointestinal bleeding carries a much worse prognosis than if it is due to extrahepatic lesions of the portal vein without liver disease (Reynell, 1951).

The technique should not be used if the patient has hypoprothrombinaemia or a low platelet count, or if the spleen is not palpable. It has been used in patients with a spleen of normal size, to demonstrate involvement of the splenic or portal vein by carcinoma of the pancreas or hilar lymph-glands, or to detect tumour metastases in the liver (Cooper, Brown, Stone, and Ferguson, 1953; Dogliotti and Abeatici, 1954). This procedure cannot be recommended, for it is difficult to puncture a spleen of normal size, and extravasation of the contrast material is very likely. It must be emphasized that a fine needle should be used in the injection, and respiration restricted while it is in position in the spleen. Blood must be seen to drip from the needle before the injection is made. If the contrast material passes outside the spleen, the injection should not be repeated on the same day. A biplane radiographic table, with serial films, offers advantages if all the collaterals and their mode of filling are to be demonstrated (Tori and Scott, 1953). Vessels running forward on the anterior abdominal wall, and backwards in the lumbar region, are clearly shown only in the lateral projection. These collaterals may provide difficulties in interpretation on the antero-posterior film. If such facilities are not available, one or two single plain films

may be taken at the conclusion of the injection of the contrast material. These radiographs will establish patency of the portal vein, although the full details of the collateral circulation may not be seen.

In the experimental animal intrasplenic injection causes only a small rise in the portal venous pressure (Dreyer, 1954). Therefore the filling of vessels other than splenic or portal veins at transplenic portal venography implies that the flow in these channels is actually retrograde, and not simply reversed by the force of the injection. On the other hand, when venography is performed at operation, the contrast medium is injected at great pressure directly into the portal vein tributary, the portal venous pressure rises, and there is extensive filling of the portal venous bed, making the resultant venograph difficult to interpret. Thrombosis of the portal vein is also a possible complication of this procedure.

In the normal portal venogram, in contrast to that seen in portal venous obstruction, only the splenic or portal vein and its intrahepatic radicles are outlined, and the contrast medium is not diverted into other channels. The blood-flow in the portal vein is said to be streamlined, that from the spleen deviating to the left side of the liver and that from the superior mesenteric vein tending to move to the right side (Sérégé, 1901). This hypothesis is used to explain the localization of disease in the lobes of the liver. Hydatid cysts, amoebic abscesses, and suppurative pylephlebitis are much commoner in the right than in the left lobe, because the primary infection is carried by the mesenteric veins and the right portal stream to the right lobe of the liver. Although the fact of portal streamlining has been established in the dog (Hahn, Donald, and Grier, 1945) it could not be confirmed in man. Injection of the contrast material into the spleen reached both lobes of the liver, the right in fact being more filled than the left. A clear area in the venogram on the right side of the portal vein may be seen where the superior mesenteric venous blood meets that from the splenic vein (Dreyer, 1954), and this should not be confused with a portal venous thrombosis. Presumably streamlining occurs at the origin of the portal vein, but the channels mix before the blood reaches the liver.

In intrahepatic portal obstruction due to cirrhosis all the splenic and portal venous blood does not pass through the liver, but some is diverted into collateral channels. In the perfused cirrhotic liver this diverted blood amounts to 87 per cent. of the portal blood-flow (McIndoe, 1928). The development of this extensive collateral circulation was clearly demonstrated in portal venograms. The sites corresponded to those seen by post-mortem dissection, and included veins around the cardia and oesophagus, para-umbilical veins, and retroperitoneal veins (McIndoe, 1928). The group of veins which carry blood from the splenic vein to the left renal vein (Learmonth, 1947) could also be demonstrated. The extent of the development of alternative pathways for portal venous blood was quite remarkable. In the present series distortion of the intrahepatic vascular pattern was often seen in cirrhosis, but its absence did not exclude this diagnosis. Comparison of the gross appearances of the liver at autopsy or operation with the venographic findings was often surprising. A finely nodular liver had

sometimes produced a normal intrahepatic pattern in the venogram. It is likely that the venogram showed only the larger dilated vessels, and that the minute distorted veins were not visible. Pre-hepatic diversion of contrast material will also lead to diminished intrahepatic filling.

The diagnosis of extrahepatic portal obstruction has hitherto been possible only at laparotomy, although its presence might be suspected from the combination of a raised intrasplenic pressure with normal occluded hepatic vein pressure (Atkinson and Sherlock, 1954). Portal venography enables a diagnosis to be made with certainty, and the site of the obstruction to be accurately localized. If the splenic vein is blocked the venogram, of course, will only demonstrate the proximal end of the occlusion, and its extent cannot be determined. In extrahepatic portal vein obstruction the collateral circulation on the whole showed a similar pattern to that described in the group of patients with intrahepatic obstruction. The para-umbilical veins fill from the left branch of the portal vein, and were therefore not demonstrated. Additional prominent collaterals were large lumbar veins, which eventually drained into the inferior vena cava, forming a natural portal-lumbar-caval anastomosis. The demonstration of these channels was of considerable importance to the patient. Splenectomy was excluded, for it would necessarily have entailed section of these valuable and benign collaterals. In all the patients who had extrahepatic portal venous obstruction the part of the splenic or portal vein remaining patent was inadequate for any anastomotic operation. Venography therefore prevented a fruitless surgical exploration.

The commonest cause of portal hypertension is portal cirrhosis, and it is the condition in which operation is most often considered. Thrombosis of the portal vein virtually prohibits anastomotic operation, and it is interesting that this complication was found in four of the 20 patients with cirrhosis. This finding agrees well with the incidence of 11 per cent. reported by Hunt and Whittard (1954). Thrombosis is presumably related to the slow portal blood-flow and phlebosclerosis of the portal vein which occur in the cirrhotic patient. Chronic neurological complications are particularly common in association with portal venous thrombosis (Sherlock, Summerskill, White, and Phear, 1954). The use of portal venography to demonstrate this lesion may elucidate unexplained neurological symptoms in patients with liver disease. Ahrens, Payne, Kunkel, Eisenmenger, and Blondheim (1950) have postulated the development of intrahepatic portal hypertension in patients with biliary cirrhosis. Collateral channels were clearly demonstrated in the venogram even in quite early stages of the disease.

Portal venography will demonstrate systemic collateral channels which cannot be demonstrated by other means. Barium swallow examination reveals only a proportion of oesophageal varices. Templeton (1944), comparing findings at autopsy with the results of barium swallow examinations done within a year of death, found that only 40 per cent. of oesophageal varices were detected by this means. In a similar study Hare, Silveus, and Ruoff (1948) found that examination by barium swallow revealed only 15 per cent. of varices. Brick

and Palmer (1953) found varices by this method in only 19 of 92 patients in whom they had been seen at oesophagoscopy. In the present series barium swallow examination demonstrated 59 per cent. of oesophageal varices found at portal venography. Oesophagoscopy is a much more reliable method of detecting oesophageal varices, but even so failed in three of 18 examinations. Outlining of portal systemic collateral channels implies the presence of portal hypertension, and in no instance were they present with a normal portal venous pressure. Portal hypertension, however, can occur with a normal portal venogram, and sometimes with a higher pressure than that found in patients with a well-marked collateral circulation. It therefore seems likely that the time factor is of importance in the development of these channels.

Giges and Teschan (1952) considered that the speed of flow in the portal circulation was inversely proportional to the portal venous pressure, but we could not confirm this view, as a raised portal pressure often occurred with a normal spleen-to-liver circulation time. Slowing of the portal circulation was found only when collateral channels had appeared, a result which is in agreement with findings in the experimental animal (Daniel, Prichard, and Reynell, 1952). This prolongation of the spleen-to-liver time was not simply due to less contrast medium passing through the liver, as the flow in the splenic and portal veins was also retarded. Hunt (1954) measured the speed of flow in the portal circulation at operation by injecting radioactive sodium into a jejunal vein, and recording its passage along the portal vein with a double-probe scintillation detector. His results led him to postulate that portal stasis is of greater importance than portal hypertension in producing the clinical picture of portal obstruction. We have never found stasis in the absence of portal hypertension, although it was present in every patient who had developed symptoms of portal obstruction, and to this extent its importance has been confirmed.

We are indebted to Mr. Sol Cohen, Dr. George Ormiston, Dr. J. D. Paulett, and Dr. B. F. G. Swynnerton for referring patients to us. We wish to thank Mr. C. R. Brecknell and his staff for photographic assistance.

Summary

The results of investigation of the portal circulation are discussed. They relate to 35 patients, comprising 21 with portal cirrhosis, seven with biliary cirrhosis, two with obstruction of the splenic or portal veins in the absence of liver disease, and five with splenomegaly of various sorts without portal hypertension.

A safe technique for percutaneous trans-splenic portal venography is described, and the indications for its use outlined.

In the normal portal venogram only the splenic vein and portal vein, with its intrahepatic ramifications, are outlined. With intrahepatic portal venous obstruction a proportion of the flow by-passes the liver through collateral channels, of which the left gastric vein, leading to gastric and oesophageal veins, was the most common. Para-umbilical veins, the inferior mesenteric vein, and

vessels running from the spleen to the diaphragm and parietes, were also outlined. Lumbar veins were particularly prominent in the presence of extrahepatic portal obstruction.

Portal vein thrombosis is a common complication of portal cirrhosis, and was found in four of 20 patients. There was a high incidence of portal obstruction in biliary cirrhosis; of the seven patients studied, three had intrahepatic obstruction, and a fourth had splenic vein thrombosis.

Portal venography revealed a greater percentage of oesophageal varices than either barium swallow examination or oesophagoscopy, alone or in combination.

The venographic demonstration of a collateral circulation is conclusive evidence of portal hypertension, although a raised portal venous pressure may be found in patients with a normal portal venogram.

Slowing of the portal blood-flow occurs whenever collateral channels are present, but is not a feature of portal hypertension alone.

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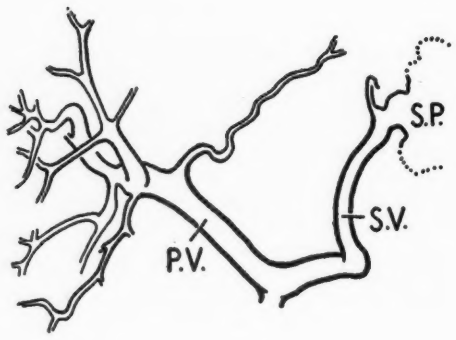

FIG. 2. Case 31. Normal portal venogram. The splenic vein, portal vein, and intrahepatic branches are clearly outlined. No collaterals are present.

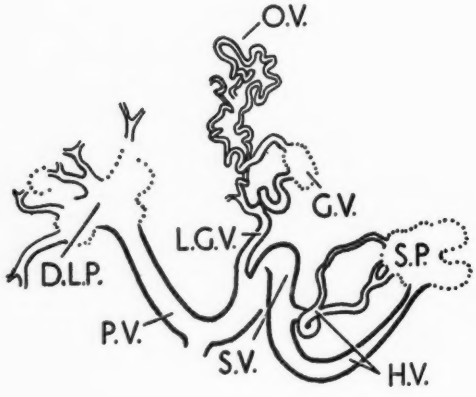

FIG. 3. Case 3. Portal cirrhosis. The splenic and portal veins are patent. The intrahepatic portal radicles are irregular and distorted. There is extensive filling of the left gastric and para-oesophageal veins (this patient had a successful portocaval shunt operation).

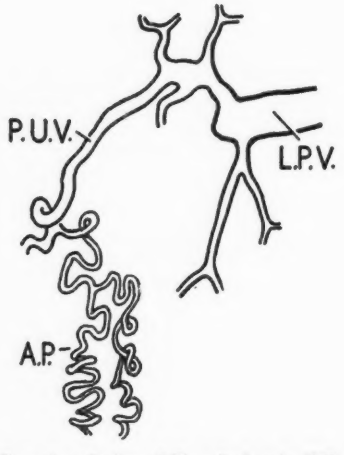

FIG. 4. Case 11. Portal cirrhosis. The lateral radiograph demonstrates vessels in the anterior abdominal wall. A para-umbilical vein is seen to arise from the left portal vein.

S.P.: pool of contrast medium in splenic pulp. H.V.: hilar veins of spleen. S.V.: splenic vein. P.V.: portal vein. L.P.V.: left branch of portal vein. D.L.P.: distorted intrahepatic portal vasculature. L.G.V.: left gastric vein. G.V.: gastric veins. O.V.: para-oesophageal veins. P.U.V.: para-umbilical vein. A.P.: venous plexus in anterior abdominal wall.

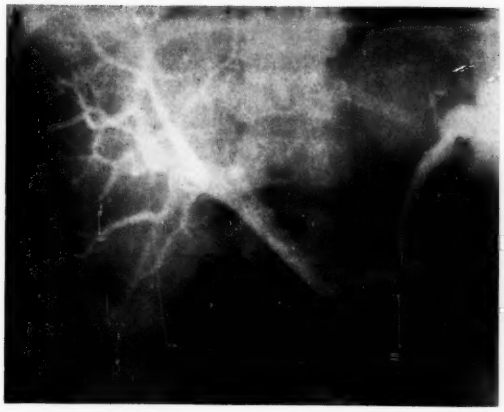

FIG. 2

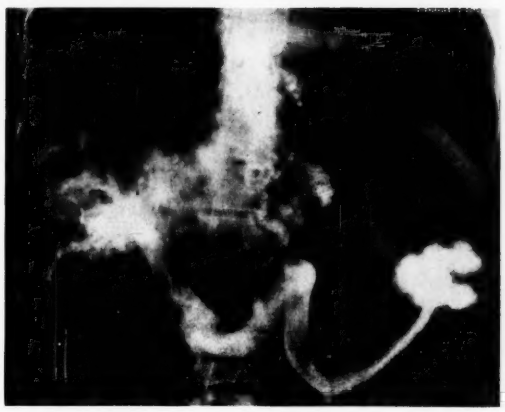

FIG. 3

FIG. 4

FIG. 5*a*

FIG. 5*b*

FIG. 6

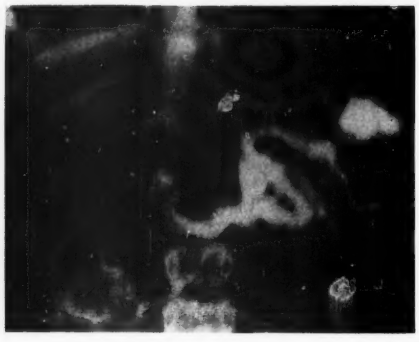

FIG. 7*a*

FIG. 7*b*

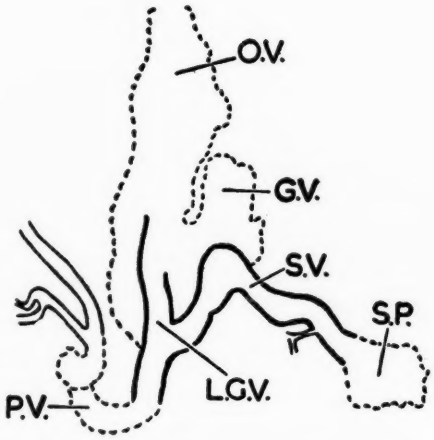

FIG. 5a. Case 29 (anteroposterior radiograph). Portal cirrhosis and partial portal vein thrombosis. Through the left gastric vein very large para-oesophageal veins are filled. The portal vein is partly obliterated, and it appears that some intrahepatic branches have filled through the recanalized portal vein.

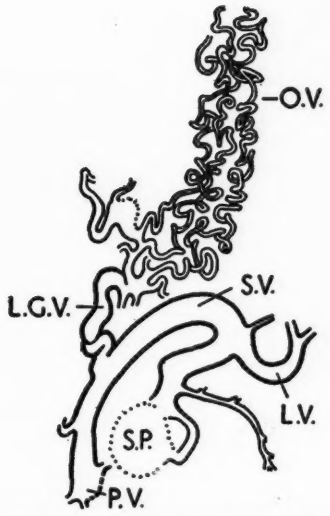

FIG. 5b. Case 29 (lateral radiograph). The collateral and oesophageal veins are clearly shown. Some lumbar paravertebral veins are outlined posteriorly and appear to fill from the splenic and parasplenic veins.

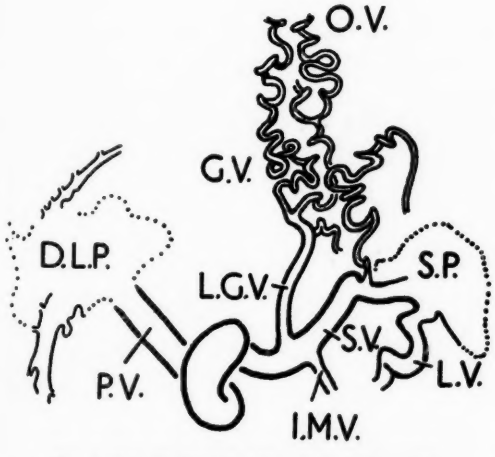

FIG. 6. Case 23. Partial obliteration of the portal vein at the porta hepatis. There are extensive parasplenic collateral vessels. The left gastric, para-oesophageal, and subdiaphragmatic communications are clearly outlined. The intrahepatic portal radicles are grossly distorted and inadequately filled. This patient had a successful portocaval shunt operation.

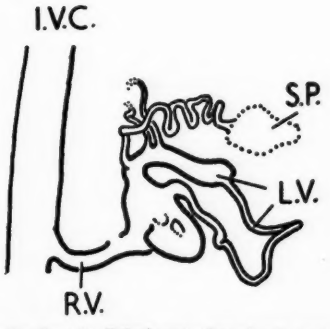

FIG. 7a. Case 24. Splenic vein thrombosis. Anteroposterior view showing a short splenic vein with very tortuous collateral channels and filling of the inferior vena cava.

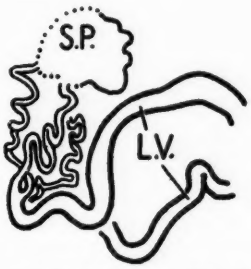

FIG. 7b. Case 24. Splenic vein thrombosis. The lateral film shows extensive tortuous collateral lumbar and paravertebral veins.

See key to Plate 7: L.V.: lumbar veins. I.M.V.: inferior mesenteric vein. R.V.: left renal vein. I.V.C.: inferior vena cava

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THE VALUE OF BARBITURATE ESTIMATIONS IN THE DIAGNOSIS AND TREATMENT OF BARBITURATE INTOXICATION[1]

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The diagnosis of barbiturate poisoning and the evaluation of different modes of therapy have always been hindered by lack of precise information regarding the amount of barbiturate absorbed and its subsequent behaviour in the body. Though methods of barbiturate analysis were widely used before the introduction of ultraviolet spectrophotometric techniques by Stuckey (1940, 1941, 1942 *a*, *b*) and Elvidge (1940), the results obtained were not sufficiently specific or quantitatively accurate to be of much practical use. Techniques for the estimation of thiopentone in blood were evolved by Hellman, Shettles, and Stran (1943) and Jailer and Goldbaum (1946), but only a little over six years has elapsed since the first spectrophotometric estimations of ordinary barbiturate derivatives were made on the blood in human cases of poisoning (Goldbaum, 1948; Walker, Fisher, and McHugh, 1948). Since 1948 a number of modified methods of barbiturate assay have been published (Born, 1949; Lous, 1950; Goldbaum, 1952; Wright and Johns, 1953), and a considerable amount of data has accumulated which indicates that, for a given barbiturate derivative, a simple quantitative relationship exists between its concentration in the blood and the clinical effect produced. The present paper contributes further data, and enables certain observations to be made about the value of the main therapeutic procedures.

Materials and Methods

Material for barbiturate analysis was obtained from patients admitted to the London Hospital between June 1951 and June 1954 (Cases 1 to 27), and from specimens taken at autopsy from 18 fatal cases in the London area over a considerably shorter period (Cases 28 to 45). The great majority of persons in both these groups had taken overdoses of barbiturates with suicidal intent or as a suicidal gesture. Clinical details are summarized in Table I. Material was also collected from patients in hospital undergoing treatment with barbiturates. Clinical details are recorded in the text where relevant. The quantitative ultraviolet spectrophotometric procedure used in all cases has already been published (Wright and Johns, 1953), and some of the results recorded in that paper are included in the present work. Until January 1953 the qualitative methods used involved extraction and mixed-melting-point determination or

[1] Received September 2, 1954.

TABLE I

Case number	*Age (years)*	*Sex*	*Drug*	*Initial blood level (mg./100 ml.)*	*Clinical state*	*Treatment**	*Time taken for recovery (hours)†*	*Blood level on recovery of of consciousness (mg./100 ml.)*	*History*
1	52	M	Phenobarbitone	12·3	Very deep coma. Cyanosis	G.L. Picrotoxin 477 mg. in 47 hrs.	47	5·2	Thought to have taken 19,500 mg. phenobarb. more than 24 hrs. previously
2	80	F	,,	11·6	,, ,,	G.L. Picrotoxin 2,508 mg., amphetamine 830 mg. in 240 hrs.	250 (death)	*Post mortem* 3·3	Last seen conscious 15 hrs. previously. No gross abnormality *post mortem*
3	64	M	Phenobarbitone, alcohol, and ? other poison	9·0	Moderately deep coma	G.L. (91) Supporting therapy	13 (death)	*Post mortem* 7·0	Seen to fall unconscious in street 20 hrs. previously. Mouth and hands stained with green vomitus. *Post mortem*: asphyxia from inhaled vomit
4*a*	43	M	Phenobarbitone	8·6	,, ,,	G.L. (traces) Picrotoxin 10·5 mg., nikethamide 3·4 mg. statim	39	6·6	Epileptic. Took 2,730 mg. phenobarb. about 4 hrs. before admission
4*b*	44	M	,,	12·1 (Maximum 13·6 52 hrs. later)	Deep coma	G.L. Picrotoxin 681 mg. in 70 hrs.	96	9·3	Same patient as Case 4*a*, 9 months later. Took large dose of phenobarb. about 2 hrs. before admission
5	42	M	,,	7·6	Stuporose. Gross ataxia	Supporting therapy only	..	..	Epileptic, recently receiving increasing doses of phenobarb. to control fits
6	44	M	,,	5·2	Light coma	Supporting therapy only	2	5·2	Epileptic. Found at foot of flight of stairs. ? Head injury
7	40	F	Phenobarbitone and amylobarbitone	4·1 (as phenobarb.)	Moderately deep coma	G.L. Nikethamide 4 ml. intravenous	12	3·0	Took 780 mg. phenobarb. and 585 mg. amylobarb. 5½ hrs. before admission
8	26	F	Phenobarbitone	3·2	Very drowsy. Ataxic	G.L. (17) Supporting therapy	..	..	Took handful of tablets about 20 hrs. before admission
9	43	F	,,	3·4	Very drowsy. Ataxic	G.L. Supporting therapy	..	..	Took 1,170 mg. phenobarb. about 5½ hrs. before admission
10	46	F	,,	3·2	Drowsy. Ataxic	G.L. (114) Supporting therapy	..	..	Epileptic. Took 1,300 mg. phenobarb. 24 hours previously. G.L. within 20 mins.
11	19	F	,,	2·8	Stuporose. Gross ataxia	G.L. (130) Supporting therapy	..	..	Took 1,105 mg. phenobarb. 2 hrs. previously
12	70	F	,,	2·3	Moderately deep coma	Supporting therapy only	24	1·6	Found unconscious with head in gas oven. Taps not turned on. No carboxyhaemoglobin in blood. Later showed Parkinsonian features

* G.L. = gastric lavage. Figures in parentheses = mg. of barbiturate recovered.

† These times relate to the interval after the first blood sample was taken, in some cases several hours after admission.

TABLE I (*contd.*)

Case number	*Age (years)*	*Sex*	*Drug*	*Initial blood level (mg./100 ml.)*	*Clinical state*	*Treatment**	*Time taken for recovery (hours)*†	*Blood level on recovery of consciousness (mg./100 ml.)*	*History*
13	31	F	Phenobarbitone	1·0	No symptoms or signs	G.L. (364) Supporting therapy	..	..	Took handful of phenobarbitone tablets 12 hrs. previously. G.L. within 20 min.
14	69	M	Barbitone, hashish, and alcohol	10·7	Stuporose. Gross ataxia	G.L. Supporting therapy	..	..	Found unconscious 30 hrs. previously
15	50	F	Barbitone	8·3	Light coma	G.L. Supporting therapy	27	7·2	Took 3,995 mg. sodium barbitone 21 hrs. previously
16	51	M	,,	7·0	Very drowsy. Gross ataxia	Supporting therapy only	..	..	Had received 650 mg. sodium barbitone nightly for 6 months. Took 3,250 mg. night before admission
17	23	M	Butobarbitone	4·3	Deep coma	G.L. Picrotoxin 26 mg. in 15 hrs.	15	3·4	Took 1,853 mg. butobarb. 7 hrs. previously
18	70	F	,,		Deep coma. Severe shock	G.L. Picrotoxin 190 mg. in 11 hrs.	11	<3·7	Subject to Parkinsonism. Took 585 mg. butobarb. 2 hrs. before admission
19	26	F	,,	3·3	Light coma	G.L. Supporting therapy	23	2·3	Alleged to have taken large dose about 12 hrs. previously
20	25	M	,,	2·0	Drowsy. Ataxic	G.L. Supporting therapy	..	..	Took 1,950 mg. butobarb. 20 hrs. previously
21	54	M	Amylobarbitone and 2 bottles of whisky	2·5	Deep coma	G.L. Picrotoxin 18 mg. in 1½ hrs.	20	1·5	Thought to have taken 1,500 mg. a few hrs. previously. Recent pneumonectomy for carcinoma
22	31	F	Amylobarbitone and brandy	2·4	Deep coma. Severe shock	G.L. Picrotoxin 52 mg. in 1½ hrs.	13	..	Took 1,853 mg. amylobarb. and half a bottle of brandy 12 hrs. previously
23	23	M	Amylobarbitone	1·0	Light coma	G.L. (292) Supporting therapy	6	..	Alleged to have taken 3,900 mg. sodium amytal 4 hrs. previously
24	51	F	Amylobarbitone and quinalbarbitone	3·2	Deep coma. Severe shock	G.L. (100) Picrotoxin 7·5 mg. statim	3	..	Found lying in garden at 8.30 a.m. Thought to have taken 4,385 mg. amylobarb. and 292 mg. quinalbarb. 11 hrs. before admission
25	43	M	,, ,,	1·3 (as amylobarb.)	Light coma	G.L. Supporting therapy	20	0·6	Took 1,350 mg. amylobarb. and 1,350 mg. quinalbarb. 42 hrs. previously
26	25	M	Quinalbarbitone	1·9	Moderately deep coma	G.L. (>613) Picrotoxin 55·5 mg. in 13 hrs.	24	0·6	Took 3,900 mg. quinalbarbitone 13 hrs. previously. G.L. within 2 hrs.
27	34	M	Pentobarbitone	1·0	Very drowsy. Gross ataxia	G.L. Supporting therapy	..	..	Took unspecified dose of pentobarb. 36 hrs. previously

* G.L. = gastric lavage. Figures in parentheses = mg. of barbiturate recovered.
† These times relate to the interval after the first blood sample was taken, in some cases several hours after admission.

TABLE I (*contd.*)

Case number	*Age (years)*	*Sex*	*Drug*	*Blood level (mg./100 ml.)*	*History*	*Post-mortem findings**
28	55	M	Phenobarbitone	8·2	Found dead in bed. Last seen apparently asleep 5 hrs. previously	No obvious cause of death. Stomach (205)
29	66	M	,,	7·9	Found dead in bed. Last seen apparently asleep 4 hrs. previously	Hepatic cirrhosis. Very cyanotic. Pulmonary congestion. L. ventricle enlarged
30	63	M	Phenobarbitone and carbon monoxide	Heart blood 4·8 Hepatic vein blood 5·3	Found with head in gas oven. Last seen alive 8 hrs. previously	Blood carboxyhaemoglobin 40 %
31	46	M	Phenobarbitone	..	Found dead in his office. Last seen alive 24 hrs. previously	Congestion and oedema of brain and lungs. Stomach (1,040)
32	64	F	Barbitone	..	Found dead in bed. Last seen alive 8 hrs. previously	Congestion of brain and lungs. Moderate hypertrophy of L. ventricle. Gross occlusion of L. coronary artery. Stomach (372)
33	72	M	,,	..	Found dead in bed. Took 14,600 mg. sodium barbitone 24 hrs. previously	Oedema of lungs. Gross hypertrophy of L. ventricle. Small left kidney. Stomach (153)
34	67	F	Butobarbitone	7·1	Recent hemiplegia. Found in deep coma. Died in another hospital 13 hrs. later	Moderate hypertrophy of L. ventricle. Moderate coronary atheroma. Stomach (trace)
35	?	M	Cyclobarbitone	12·1	Found dead in bed	No details
36	50	F	Amylobarbitone	17·7	Asthmatic. Found sitting dead on the steps of a police-station	Brain, lungs, and kidneys congested. Stomach (315)
37	69	F	,,	4·1	Hypertensive. Found dead in bed. Last seen alive 4 hrs. previously	Congestion and oedema of brain and lungs. Slight cardiac enlargement. Stomach (1,182)
38	?	M	,,	3·0	Found dead	No other details. Stomach (1,120)
39	24	M	Amylobarbitone and quinalbarbitone	9·0	Recently suffering from painful neuroma of wrist. Found dead. Last seen alive more than 12 hrs. previously	No obvious cause of death. Stomach (289)
40	?	M	,, ,,	2·5	Found dead	No details. Stomach (771)
41	71	F	Pentobarbitone	7·5	Hypertensive. Found dead in bed. Last seen alive 7 hrs. previously	Brain and lungs congested and oedematous. Moderate coronary atheroma. Stomach (385)
42	26	M	Pentobarbitone and alcohol	3·9	Athlete. Found dead in bed. Last seen alive 8 hrs. previously	Congestion and oedema of lungs and brain. Stomach (7·4)
43	50	F	Pentobarbitone	3·8	Found dead in bed. Last seen alive 8 hrs. previously	Congestion and oedema of lungs
44	54	F	,,	3·3	Diabetic. Recent coronary thrombosis. Found dead in bed. Last seen alive 14 hrs. previously	Congestion and oedema of lungs. L. ventricle hypertrophied. Moderate coronary atheroma. Slightly contracted kidneys. Stomach (133)
45	35	F	,,	2·4	Seen to fall unconscious. Died before arrival in hospital	Brain and lungs congested

* Figures in parentheses = mg. of barbiturate recovered.

microcrystalline appearance (Turfitt, 1948); after that time paper chromatography (Wright, 1954) has been used exclusively, and it has also been possible to check the results in earlier cases by using blood specimens which had been stored in a refrigerator for periods up to 18 months.

Correlation of Blood Barbiturate Levels with Clinical State

The relationship between blood-barbiturate levels and the degree of depression of the nervous system produced is illustrated somewhat broadly in Fig. 1. Deep coma implies profound unconsciousness with absence of all reflexes; light coma indicates unconsciousness with retention of reflexes and some measure of

response to painful stimuli. Waking is defined as the capacity of the patient to articulate his name or a short sentence coherently when pressed to do so. The

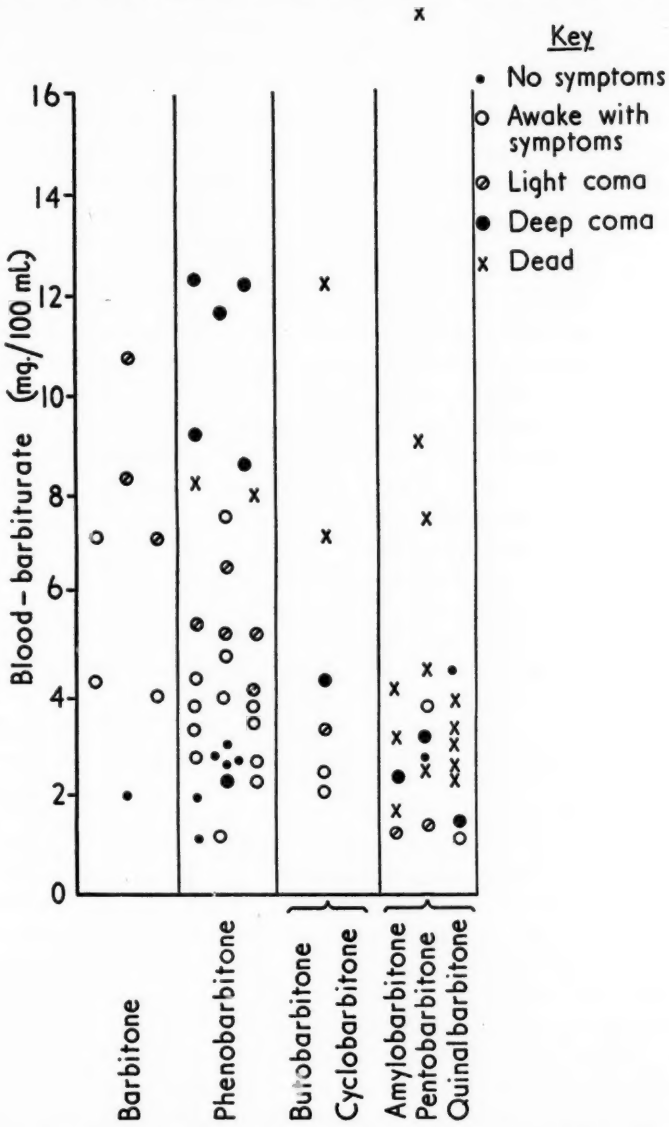

FIG. 1. Correlation between the blood-barbiturate level and the clinical state. Blood levels estimated during analeptic therapy are not included.

process of further recovery is associated with dysarthria, ataxia, and nystagmus, and the patient often complains of double vision and severe headache. Obviously there are wide variations in depression in each of the above categories, and the

grading of severity is simply for the purpose of graphic representation. The observations made on barbitone poisoning, although relatively few, indicate that blood values in excess of 10 mg. per 100 ml. are required to produce deep coma, the transition between light coma and stupor occurring in the range 9 to 7 mg. per 100 ml. With phenobarbitone a larger number of observations were made; the transition from deep to light coma occurs in the range 9 to 7 mg. per 100 ml., and from light coma to stupor in the range 6 to 4 mg. per 100 ml., for most cases. In coma due to short-acting barbiturates much lower blood levels, of the order 1 to 3 mg. per 100 ml., were observed, and the majority of persons found dead after ingestion of these drugs had blood levels of the order 2 to 5 mg. per 100 ml., though, where massive doses were rapidly fatal, much higher blood levels were recorded (Cases 36, 39, and 41). Other workers have reported similar results in correlating blood-barbiturate levels and clinical states (Goldbaum, 1948; Fisher, 1949; Roche, Wynne, and Haskins, 1950; Nilsson, 1951), but several factors may operate in individual cases to produce anomalous results; these are tolerance, intercurrent disease and senility, and the concurrent administration of other noxious substances. Above all, the presence of anoxia and shock may greatly increase the apparent depressive effect of barbiturates.

Tolerance. Continuous administration of both long- and short-acting barbiturates undoubtedly leads to tolerance, but the present evidence suggests that, for phenobarbitone at any rate, such tolerance is not great, no patient having so far been observed entirely free from symptoms or signs of intoxication with a blood level over 3·0 mg. per 100 ml. The only patients who retained consciousness with blood-phenobarbitone levels in excess of 5·0 mg. per 100 ml. (Cases 4*a* and 5) were both epileptics of at least 20 years' standing. Evidently greater tolerance is possible, since Fisher, Walker, and Plummer (1948) cited the case of a man aged 43 years who 'awoke', apparently without the aid of analeptics, with a blood-phenobarbitone level of 11·8 mg. per 100 ml. So-called 'acute' tolerance to large doses of barbiturate probably also occurs; indeed it has been proved to do so in the case of thiopentone (Brodie, 1952). The evidence for tolerance to short-acting barbiturates is more convincing. One psychopathic woman aged 25 years, who sought treatment for a skin rash, and who admitted taking up to 30 gr. of amylobarbitone a day for several months, had a blood level of 4·2 mg. per 100 ml.; she was alert, and the only neurological abnormality was slight nystagmus. Of patients receiving continuous narcosis with six-hourly doses of amylobarbitone ranging from 5 to 10 gr., one man remained alert with a blood level of 2·3 mg. per 100 ml., and one woman was drowsy and ataxic with a blood level of 3·5 mg. per 100 ml. Since blood levels of this order are commonly found in cases of fatal acute poisoning, it is important that death should not be attributed to barbiturates unless it is certain that the subject was not a barbiturate addict.

Senility and intercurrent disease. Of the three patients aged 70 years and over who were admitted to hospital, one (Case 2) had clearly taken a large overdose of phenobarbitone (blood level 11·6 mg. per 100 ml. on admission), and this

apparently resulted in irreversible cerebral damage, though she lived for 10 days; another (Case 18), subject to Parkinsonism, was said to have taken a comparatively small overdose of butobarbitone, and was very deeply unconscious for several hours. Unfortunately the blood estimation was unreliable in her case. The third patient (Case 12) was found with her head in a gas oven, but had evidently not absorbed any carbon monoxide, and the only apparent cause for her moderately deep coma was a blood-phenobarbitone level of 2·3 mg. per 100 ml.; she later exhibited signs of Parkinsonism and senile dementia. The development of Parkinsonian symptoms in patients with chronic barbiturate poisoning was noted by Stone (1936). Conversely it seems possible that patients with Parkinsonism are unduly susceptible to barbiturates. Cardiovascular disease figures prominently among the cases coming to autopsy (Nos. 29, 32, 33, 34, 37, 41, and 44); the contribution of such disease to the fatal outcome is difficult to assess, since there is evidence that large doses of barbiturate were taken in all these cases. In Case 29, a patient with coronary atheroma, ventricular hypertrophy, and hepatic cirrhosis, the blood-phenobarbitone was only 7·9 mg. per 100 ml., a level usually survived by healthy persons; in Case 32 recent coronary thrombosis was present, possibly due to temporary lowering of blood-pressure from an overdose of barbitone.

Simultaneous administration of other noxious substances. When barbiturates are taken with suicidal intent, other poisons are frequently administered as well; the commonest of these substances are carbon monoxide, salicylates, and alcohol. Examples of such combinations occur in the present series (Cases 3, 14, 21, 22, 30, and 42) but, with the exception of Case 30, in which death was probably mainly due to carbon monoxide poisoning, the blood levels were not unduly low for the degree of depression observed. In Case 3 the blood level was compatible with moderately deep coma, and the patient's death 13 hours later was due to inhalation of vomitus, though an unidentified poison may have contributed.

Shock and anoxia. Estimation of the blood-barbiturate level is obviously of value in differentiating depression due to barbiturates from secondary depression produced by shock and anoxia; the contribution these factors make in a case of coma is, however, most easily recognized by the immediate response to simple restorative measures. Post-mortem examination suggested that, when death had occurred outside hospital, anoxia secondary to asphyxia was very frequently the cause. Asphyxia may be due to inhibition of the respiratory centres by overwhelming concentrations of barbiturates, but is probably more often due to pulmonary oedema, or to suffocation by falling back of the tongue or by contact of the face with bed-clothes. In the latter circumstances it is not surprising that comparatively low blood-barbiturate levels are sometimes recorded. The shorter-acting barbiturates appear to be particularly liable to produce shock and pulmonary oedema, and it is of interest that these agents were responsible in most of the persons who died outside hospital. Patients reaching hospital tend to be selected, in that the majority are suffering from prolonged narcosis due to long-acting barbiturates. Patients admitted after

taking short-acting derivatives generally respond rapidly to simple restorative measures. Differences in the composition of various series, with regard to the proportions of patients poisoned with long- and short-acting derivatives, thus lead to differences in mortality, irrespective of the treatment used.

Analeptics

If the factors discussed in the preceding sections are taken into account, it should be possible to use the blood-barbiturate level as a criterion in assessing the therapeutic efficacy of analeptics. The data presented in this paper have been collected over a period during which analeptics have been somewhat out of favour. While this has restricted the number of observations made regarding their action, it has permitted a more extensive study of the natural history of barbiturate intoxication in the remaining cases. Picrotoxin was the analeptic of choice in the present series, and was usually given intravenously at the rate of 3 to 6 mg. every half-hour. While in each case an increase in respiratory excursion was observed after injection, there appeared to be no significant effect on blood-pressure or pulse-rate. Evidence of early awakening due to picrotoxin was obtained in only one case (No. 4*b*). This patient had been admitted nine months previously after an overdose of phenobarbitone (Case 4*a*), and on that occasion he received no analeptics other than an initial dose of 10·5 mg. picrotoxin and 3·4 mg. nikethamide; he was not rousable until his blood level fell to 6·6 mg. per 100 ml. On the second admission he had clearly taken a much larger dose of phenobarbitone; gastric lavage was imperfect, and continued absorption was manifested by a rise in the blood-phenobarbitone level, the maximum recorded being 13·6 mg. per 100 ml. over 50 hours after admission. Picrotoxin therapy was started 26 hours after admission, and the patient could be roused on the fifth day, with the blood level 9·3 mg. per 100 ml.; a further three days elapsed before the blood level fell to 6·0 mg. per 100 ml., and continued administration of picrotoxin was required during most of this time to keep the patient awake.

It is generally recognized that convulsions occurring during picrotoxin therapy of barbiturate poisoning result in increased depression of the nervous system. In Case 1 there were severe convulsions during the early stages of picrotoxin therapy, and this may have been the reason why the patient could not be roused until his blood-phenobarbitone level had fallen to 5·2 mg. per 100 ml.—a level at which spontaneous awakening might be expected. Convulsions may occur in barbiturate intoxication irrespective of the administration of analeptics; they occurred in Case 4*a* during this patient's first admission, 12 hours after administration of a small dose of picrotoxin, when his blood-phenobarbitone level was 7 mg. per 100 ml., and again shortly after his second admission (Case 4*b*), with a blood level of 12·1 mg. per 100 ml., before any analeptics had been given. Convulsions occurring under these conditions may be due to anoxia or to underlying epilepsy. On the other hand, certain barbiturates, notably phenobarbitone (Wagner, 1933; Curran, 1938), are reputed to

possess convulsive properties. It seems that a tendency to spontaneous convulsions does not necessarily potentiate the convulsive properties of picrotoxin, for in Case 4*b* picrotoxin was given over a long period without further convulsions occurring. Similarly, prolonged picrotoxin therapy did not lead to convulsions in Case 2, although they might have been expected, since the patient had probably suffered irreversible brain damage from anoxia before admission. In view of the variable response to picrotoxin in patients with phenobarbitone poisoning, the blood-phenobarbitone level is an unsuitable criterion on which

TABLE II

Distribution of Barbiturates throughout the Body-Water

(Assuming body-water = 70 per cent. total weight of body)

Case number	*Estimated volume of body-water (ml.)*	*Drug*	*Estimated quantity absorbed (mg.)*	*Calculated blood level (mg./100 ml.)*	*Highest blood level observed (mg./100 ml.)*	*Approximate time after ingestion of barbiturates (hours)*
4*a*	34,400	Phenobarbitone	2,730	8·0	8·6	4
9	33,000	,,	1,170	3·6	3·4	5½
10	41,600	,,	1,186	2·9	3·2	24
11	39,900	,,	975	2·4	2·8	2
17	42,000	Butobarbitone	1,853	4·4	4·3	7

to base picrotoxin dosage. In poisoning with short-acting barbiturates there appears to be less tendency to convulsions, even when large doses of picrotoxin are given (for example, Case 22). It is difficult to assess the waking action of picrotoxin in these cases, since blood levels tend to be at the lower limit of accurate measurement for the method used.

Barbiturates in Tissues and Tissue-Fluids

General distribution. Koppanyi, Dille, and Krop (1934) and Dille, Linegar, and Koppanyi (1935) found that barbitone was distributed generally throughout the body in dogs and rats, and that it was present in the organs as long as it was detectable in the blood; they therefore inferred that the rate of destruction of barbitone could be discovered by following its blood concentration. They refuted the evidence of Keeser and Keeser (1930) that barbitone is selectively localized in various parts of the brain, and their conclusions have recently received support from the work of Maynert and Van Dyke (1950), who used ^{15}N-labelled barbitone in dogs. It is nevertheless generally agreed (Butler, 1950; Bain, 1952) that certain barbiturate derivatives, for example pentobarbitone, appear in slightly higher concentration in brain substance than in other tissues, and that concentration of all barbiturate derivatives occurs in the liver and kidneys. The general truth of the assertion that barbiturates are distributed throughout the body-water is supported by the present investigation (Table II). In five cases for which reliable data are available, the highest blood level observed is in good agreement with the value calculated from the body-weight and the dose presumed to have been absorbed. Considering the wide assumptions made, the similarity between observed and calculated values

is remarkably close, and is of forensic value in that it enables an estimate of the ingested dose to be made from the blood level.

In determining the amount of barbiturate absorbed after a single dose, it is usually safe to assume that significant quantities of drug are unlikely to be present in the stomach after four hours (Harstad, Møller, and Simesen, 1942). In the present series this finding was confirmed in 12 cases in which gastric

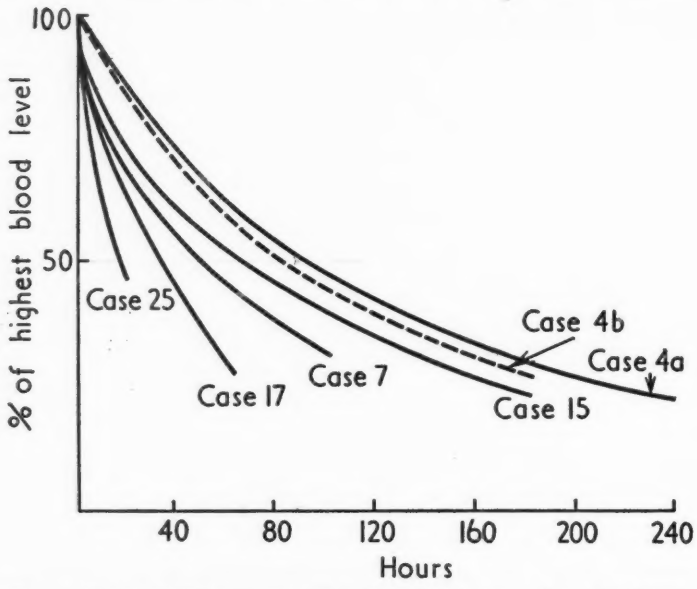

FIG. 2. Rate of disappearance of various barbiturates from the blood. Case 4*a*, 4*b*, phenobarbitone. Case 15, barbitone. Case 7, phenobarbitone and amylobarbitone. Case 17, butobarbitone. Case 25, quinalbarbitone and amylobarbitone.

washings were analysed. Appreciable quantities (over 200 mg.) of barbiturates were present in gastric washings of three patients (Cases 13, 23, and 26) out of six seen within four hours, and in none of six cases seen later than four hours, after ingestion of the drugs. This does not, however, necessarily mean that absorption is complete; indeed Bazeley and Garrard (1948) recovered recognizable tablets of phenobarbitone by colonic lavage many hours after they had been ingested. Serial blood-barbiturate levels offer the best evidence of continued absorption of the drug, and these were estimated in all cases of the present series. Rising levels were found in several cases, and in Case 4*b* the upward trend persisted for over 24 hours after admission to hospital. Gastric lavage had been somewhat cursory in this case owing to the poor condition of the patient. After the peak blood level is reached, barbiturates disappear from blood at rates which are characteristic for each derivative. Fig. 2 shows representative curves derived from serial blood levels in cases of poisoning by different derivatives. The blood levels are expressed as a percentage of the maximum

level recorded. The curves obtained on each admission in Case 4 indicate similar rates of disappearance of phenobarbitone on both occasions, being independent of the height of the initial blood level. These curves have a practical value, in that they can be used to assess the efficiency of therapy designed to hasten the elimination of barbiturate.

Liver concentration. Table III shows concentrations of barbiturates in the liver compared with the blood level in a number of fatal cases. It is apparent

TABLE III

Concentration of Barbiturates by the Liver in relation to Time elapsing between Ingestion of Drug and Death

Case number	*Drug*	*Approximate time of death after ingestion of drug (hours)*	*Blood level (mg./100 ml.)*	**Liver concentration (mg./100 ml.)*	*Liver-blood ratio*
2	Phenobarbitone	264	3·3	3·5	1·1
3	,,	34	7·0	9·2	1·3
34	Butobarbitone	22	7·1	7·1	1·0
32	Barbitone	8	..	37·5	..
28	Phenobarbitone	10	8·2	19·3	2·4
38	Amylobarbitone	<12	3·0	13·1	4·4
40	Amylobarbitone and quinalbarbitone	<12	2·5	5·3	2·1
43	Pentobarbitone	8	3·8	12·5	3·3
30	Phenobarbitone	8	4·8†	5·7	1·2

* Liver concentrations are minimum values, since they are not corrected for loss incurred in the extraction process.

† Death in this case was mainly due to carbon monoxide poisoning.

that shortly after ingestion of barbiturates quite high concentrations are found in the liver, whereas at longer intervals after ingestion these levels are of the same order as in the blood. In Case 30 it was possible to demonstrate a gradient between hepatic-vein blood and heart blood. Thus, although the liver is important in the detoxication of certain barbiturates, its protective action in overdosage is in the first instance due to storage, which prevents much of the drug from reaching the systemic circulation. Estimation of barbiturates in the liver thus gives useful information of the time elapsing between ingestion of the drug and death.

Concentration in cerebrospinal fluid. Cerebrospinal fluid was obtained in a number of cases by lumbar puncture at the same time as venous blood was collected (Table IV). In all cases the concentration in cerebrospinal fluid was significantly lower than in blood; in most cases sufficient time had elapsed since the ingestion of barbiturate for equilibrium to have been reached between blood and cerebrospinal fluid, and it seems reasonable to assume that diffusion throughout the subarachnoid space was also complete. The practical implications of these observations are, first, that cerebrospinal fluid is a less suitable fluid than blood for diagnostic purposes, and, secondly, that drainage of cerebrospinal fluid (as advocated by Purves-Stewart and Willcox in 1934, and still widely recommended in textbooks) cannot be expected to remove significant quantities of barbiturate.

Barbiturates in urine. Urine is greatly inferior to blood as a source of material

for detection of barbiturates by spectrophotometric methods. This is due mainly to the preponderance of interfering chromogens, and to a lesser extent to the low concentrations of unchanged short-acting barbiturates appearing in urine. Even when no definite peak absorption characteristic of barbiturates can be obtained on extracts, it is sometimes possible to demonstrate the presence of

TABLE IV

Failure of Concentration of Barbiturates in Cerebrospinal Fluid Relative to Blood

Case number	*Drug*	*Approximate time after ingestion of drug that samples were taken (hours)*	*Blood level (mg./100 ml.)*	*Cerebrospinal fluid level (mg./100 ml.)*	*Cerebrospinal fluid/blood ratio*
2	Phenobarbitone	264	3·3	1·1	0·33
7	Phenobarbitone and amylobarbitone	23	3·3	1·2	0·36
8	Phenobarbitone	48	2·2	1·6	0·73
12	,,	30	1·6	1·2	0·75
14	Barbitone	30	10·7	6·3	0·59
15	,,	30	8·0	5·5	0·69
16	,,	24	4·5	2·8	0·62
26	Quinalbarbitone	13	1·9	1·0	0·53

TABLE V

Renal Clearance of Barbiturates

Case number	*Barbiturate*	*Estimated time since ingestion (hours)*	*Blood-level (mg./100 ml.) (B)*	**Urine level (mg./100 ml.) (U)*	*Urine flow (ml./min.) (V)*	*Clearance (ml./min.) $\left(\frac{UV}{B}\right)$*
1	Phenobarbitone	78	8·2	14·7	0·58	1·0
		100	6·0	11·0	0·62	1·1
4*a*	,,	70	6·0	4·8	0·6	0·5
4*b*	,,	34	13·3	18·0	1·0	1·4
	,,	58	12·9	7·5	0·84	0·5
	,,	82	10·6	8·2	0·76	0·6
	,,	106	8·8	7·8	1·49	1·3
	,,	130	7·4	6·0	1·0	0·8
14	Barbitone	54	9·4	28·6	0·8	2·4
15	,,	24	7·8	54·3	0·29	2·0
16	,,	21	4·6	16·6	1·4	5·1
		106	3·5	11·2	1·4	4·5

* Uncorrected for loss of barbiturate during extraction, therefore minimum levels.

unchanged barbiturate in the urine by other methods, for example amylobarbitone by crystallization and melting point (Case 23) and butobarbitone by paper chromatography (Case 17). It has been possible, however, to determine approximate values for urine-barbiturate in some cases, and renal clearance values are given in Table V. The data, though limited, suggest that the renal clearance of barbitone is greater than that of phenobarbitone, and that the clearance of both is slightly increased at higher rates of urine flow. Even so, the amount of barbiturate cleared in this way over a 24-hour period is com-

paratively small. No significant increase in output of barbitone or phenobarbitone was noted in casual samples of urine when large doses of sodium citrate, and later ammonium chloride, were administered during the recovery stage (Cases 16 and 4*a*). Since barbiturates have antidiuretic properties (Marx, 1931; de Bodo and Bloch, 1941; de Bodo and Prescott, 1945), it is difficult to induce diuresis in the early stages of barbiturate poisoning, and the doubtful benefits of such diuresis, as indicated in the present work, are offset by the considerable risk of inducing pulmonary oedema. Forced diuresis, therefore, is not a therapeutic measure to be recommended.

I am indebted to the Physicians of the London Hospital for allowing access to their patients, to Dr. F. E. Camps for supplying post-mortem material, and to Professor Clifford Wilson and Dr. J. M. Ledingham for encouragement and advice.

Summary

1. A quantitative relationship is demonstrated between the blood concentration of barbiturate derivatives and the degree of depression of the nervous system.

2. Comparatively low blood-barbiturate levels may be associated with profound depression when the picture is complicated by shock, anoxia, the additive effect of other poisons, senility, and possibly Parkinsonism; relatively high values may be observed in patients who through continued usage are tolerant of barbiturates, or during administration of analeptics. Early awakening due to picrotoxin was obtained with certainty in only one case. The occurrence of convulsions during the treatment of barbiturate poisoning is discussed in relation to blood-barbiturate levels.

3. Barbiturates are more or less generally distributed throughout the body-water, and it is possible to calculate the approximate dose ingested from the patient's weight and the maximum concentration of barbiturate in the blood.

4. Soon after ingestion of barbiturates large concentrations occur in the liver, but these subsequently diminish to the same order as that found in the blood. Hence, in fatal cases, some estimate can be made of the time elapsing between ingestion of barbiturates and death.

5. Barbiturates appear in considerably lower concentrations in cerebrospinal fluid than in blood, and therefore the practice of lumbar puncture, for diagnostic or therapeutic reasons, is of little value.

6. Renal clearance of barbitone is greater than that of phenobarbitone, and the clearance in both cases is slightly increased at higher rates of urine flow, but apparently not significantly increased by administration of agents designed to alter the pH of the urine. The practice of forced diuresis, with its attendant risks, is therefore not justified.

7. Gastric lavage is of little value if performed more than four hours after ingestion of the drug.

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OBESITY IN CHILDHOOD[1]

A Study of the Birth Weight, the Height, and the Onset of Puberty

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Previous Studies

Of the many papers concerned with obesity in childhood, few have dealt systematically with the development of the obese child.

Birth weight. Bauer (1929) stated that the birth weight was often high, and regarded this as evidence of a constitutional origin of the obesity. Bornhardt (1936), Gordon (1937), Hering (1938), and Mossberg (1948) agreed with Bauer. On the other hand Priesel and Frey (1938) and Bruch (1939) found that birth weights of obese children did not differ from those of normal children.

Height. In 1901 Fröhlich described his classical case of a tumour in the region of the pituitary gland in a 14-year-old boy. The patient showed signs of an intracranial tumour, and was obese and sexually immature. He was probably also slightly below average height. After Fröhlich's account 'Fröhlich's syndrome' or 'dystrophia adiposo-genitalis', a term suggested by Bartels (1906), was frequently diagnosed, even in the absence of a gross lesion in the pituitary or hypothalamic region. Most cases of obesity in childhood were thought to belong to this group (Hess and Kunstadter, 1938). Keller (1927, 1929), Bauer (1929), Rosenstern (1931, 1933), Opitz (1933), and Reye (1935) noted that obese children tended to be above average height, and regarded this as evidence against a diagnosis of 'dystrophia adiposo-genitalis'. Ellis and Tallerman (1934), Bornhardt (1936), Nobécourt (1937), Hanssen (1937), Gordon (1937), Hering (1938), Bruch (1939), Kerley and Lorenze (1941), Bronstein, Halpern, and Brown (1942), Winocur (1945), Müller (1947), Mossberg (1948), and Le Marquand (1951) confirmed this finding. Published reports contain no systematic study of the gain in height during a period of weight reduction. Ellis and Tallerman (1934) suggested that too vigorous dietetic measures might remedy obesity at the expense of growth. Wilkins (1950*a*) described a four-year-old boy who, on a low-calorie, high-protein diet, failed to gain in height at the expected rate, and became extremely weak. Wilkins regarded this case as very unusual.

Onset of puberty. There is agreement that the onset of puberty in obese girls is not delayed (Ellis and Tallerman, 1934). Most observers have found an early onset (Rosenstern, 1933; Opitz, 1933; Bornhardt, 1936; Hering, 1938; Nobécourt, 1938; Bruch, 1939, 1941; Müller, 1947; Mossberg, 1948). After Fröhlich's

[1] Received August 14, 1954.

account many observers found a late onset of puberty, or deficient genital development, in obese boys (Rosenstern, 1933; Bornhardt, 1936; Hering, 1938). Bauer (1929) and Priesel and Frey (1938) were among the first to suggest that it is impossible to make a diagnosis of hypogenitalism in boys under the age of 17 years. They considered that 'dystrophia adiposo-genitalis' is a rare condition, and that most obese boys pass through a normal puberty at the usual age. Ellis

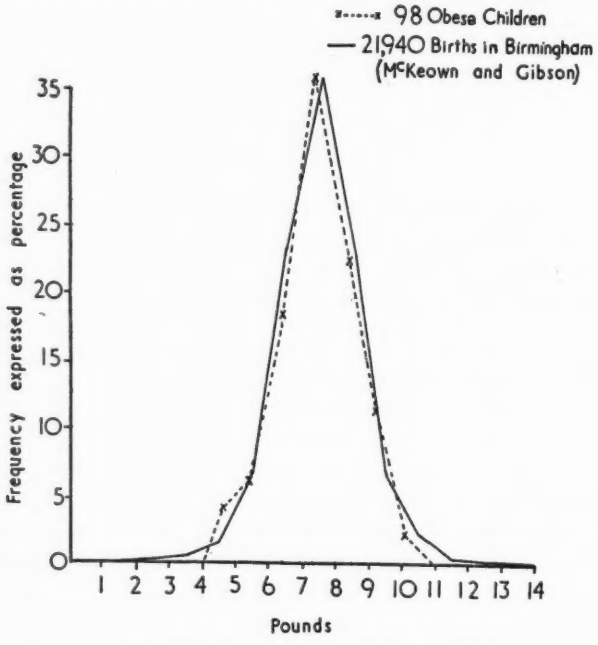

FIG. 1. Distribution curve of birth weights.

and Tallerman (1934), Chiari (1938), Nobécourt (1938), Werner (1941), Bruch (1939), and Müller (1947) came to the same conclusion. Bruch (1941) concluded that normal puberal development is the rule, but early development not uncommon. Mossberg (1948) found that obese boys, like obese girls, probably have an early onset of puberty.

Personal Observations

The present report relates to the first 100 children to attend an obesity clinic started in January 1950 at the Children's Hospital, Birmingham.

Birth weight. In all except two instances the parents were able to remember the child's birth weight. The mean birth weight for the group of 98 children was 7·4 pounds. McKeown and Gibson (1951) reported the birth weights of 21,940 children born alive in Birmingham in 1947, and found the mean birth weight to be 7·5 pounds. Fig. 1 shows the distribution curves of the birth weights of the 98 obese children and of those in McKeown's and Gibson's series. The shapes of the two curves are remarkably similar. It is concluded that the birth

weights of these 98 obese children did not differ significantly from those of the standard group. When the group of 98 obese children is divided according to the degree of obesity, the mean birth weight of the more obese group is not significantly higher than that of the less obese group.

Height. Two of the 100 children are excluded from this part of the study—a dwarf, and a child who had severe wasting of both lower limbs resulting from poliomyelitis. In the absence of a recent English height standard covering the whole of childhood and adolescence, Engelbach's tables (Engelbach, 1932) as adapted by Wilkins (1950*b*) were used for comparison. Wilkins found these tables adequate for his studies of development. Engelbach's standard agrees closely with Daley's (1950) measurements of London school-children. Figs. 2 and 3 compare the height-for-age curves of the 98 obese children with Engelbach's standard curves. The height of the obese children was on an average 1·6 inches above the standard. This difference is statistically highly significant (even calculated on the largest standard deviation for either sex and covering the whole age range, t is over 5).[1] Both Engelbach's and Daley's standards are based on measurements of children from all social classes. Figs. 4 and 5 compare the height-for-age curves of the 98 obese children with those given by Widdowson (1947) for children of the professional class. The average obese child was 0·3 inch taller than the average child of the professional class. This difference is not statistically significant ($t = 1{\cdot}29$).[2]

Gain of height by the obese children during a period of weight reduction. For this investigation the data are confined to children who have been followed up for more than six months. The dwarf and the boy who had had poliomyelitis are again excluded. The study is based on measurements of the height and weight of 82 children (33 boys and 49 girls) at the first and last examination. The weight-reducing diet contained approximately 1,000 Calories and 50 to 60 grammes of protein per day. In most cases amphetamine sulphate, 5 to 10 mg. half an hour before breakfast and the midday meal, was prescribed. Overweight has been estimated by comparing the actual weight with the standard weight for the child's height and sex, and expressing the result as a percentage. For comparison Engelbach's weight-for-height tables were used. At the first examination every child's weight was at least 30 per cent. above the standard for height and sex. The average interval between the first and last examinations was 17 months. An example will best explain the method used:

A girl aged three years and nine months at the time of the first examination.
Date of first examination: January 23, 1950.
Height: 41 inches. Weight: 55 pounds.
Standard weight for a girl 41 inches tall: 36·2 pounds.

$$\text{Percentage overweight for height: } \frac{55-36{\cdot}2}{36{\cdot}2} \times 100 = 52.$$

[1] For the calculation of the significance of this difference the standard deviation as given by Daley (1950) is used, as Engelbach's tables do not give standard deviations.

[2] For the calculation of the significance of this difference Widdowson's standard deviations for all social classes are used, as standard deviations for only the professional class are not given in her paper.

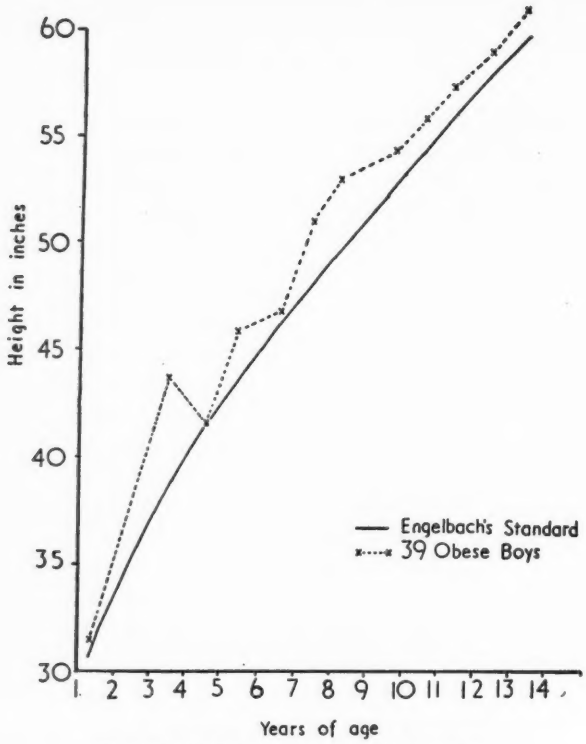

FIG. 2. Height of boys in relation to age.

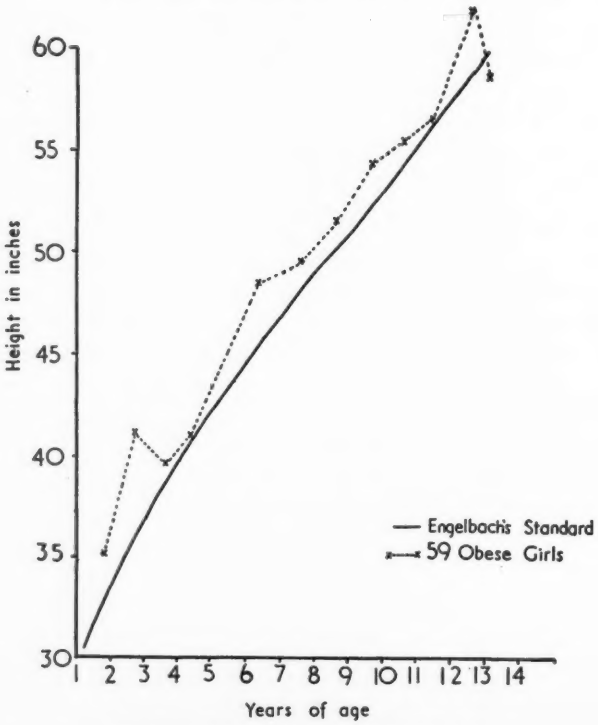

FIG. 3. Height of girls in relation to age.

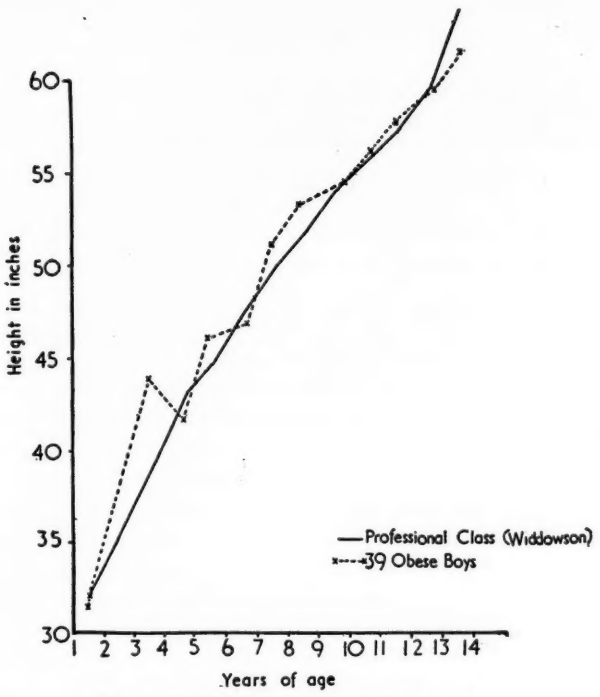

FIG. 4. Height of boys in relation to age.

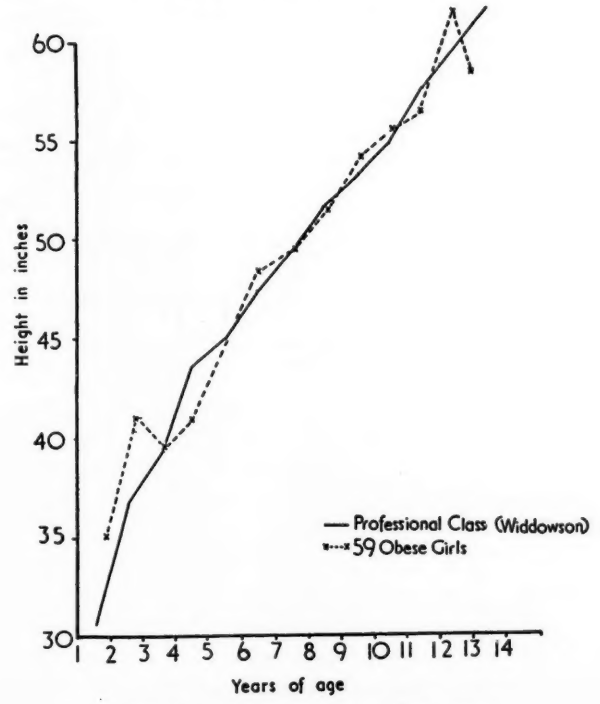

FIG. 5. Height of girls in relation to age.

Date of final examination: June 5, 1951.
Height: 44·5 inches. Weight: 53 pounds.
Standard weight for a girl 44·5 inches tall: 42 pounds.

Percentage overweight for height: $\frac{53-42}{42} \times 100 = 26.$

Weight loss during 16 months: 52—26 = 26 per cent. of standard weight.

Rate of weight loss $= \frac{26}{16} = 1{\cdot}6$ per cent. of standard weight per month.

During these 16 months she had gained 3·5 inches in height. According to Engelbach's standard a girl aged three years and nine months would be expected to gain 3·5 inches during the ensuing 16 months. It is concluded that this girl, despite a weight loss at an average rate of 1·6 per cent. of her standard weight per month, had gained in height at the expected rate.

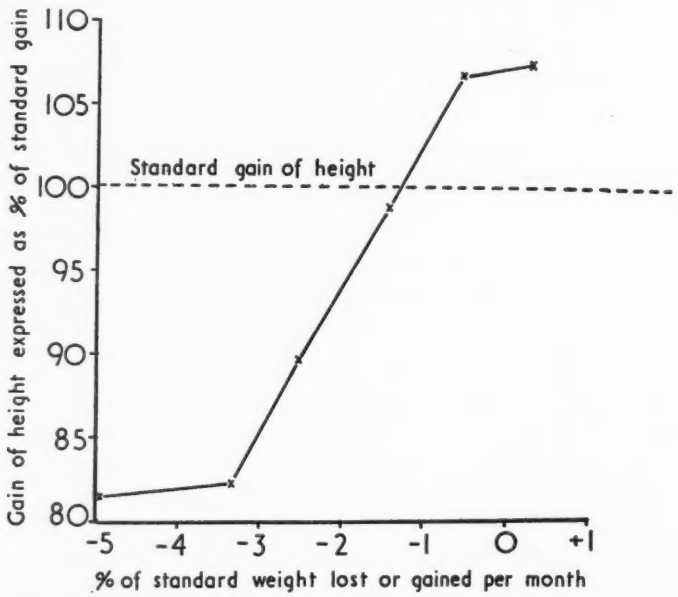

FIG. 6. Gain of height related to loss or gain of weight in 82 obese children.

It is important to stress the fact that the calculations are based on objective data, that is on measurements of height and weight, and not on the assumption that every child followed the prescribed diet. In fact, some failed to diet and to lose weight. They must be regarded as therapeutic failures; yet, for the present investigation, they serve a purpose as a group whose gain in height can be compared with that of the children who lost weight during the period of observation. In Fig. 6 gain in height has been plotted against loss (or gain) of weight. The figure shows that the gain in height of the children who lost weight most rapidly was less than the expected gain, while the gain in height of the children who lost weight slowly or not at all was above the expected rate. A

close and direct correlation is demonstrated between the rate of loss of weight and the failure to gain in height at the expected rate. For the statistical analysis the series was divided into two groups of 41 children each. The first group had lost weight at an average monthly rate of 2 per cent. or more of their standard weight. The second group had lost weight at a rate of less than 2 per cent., or had failed to lose or had gained weight. The mean age and the sex distribution of the two groups was similar. The first group had made 14·8 per cent. less than the expected gain in height; the second group gained in height 4·6 per cent. more than expected. The difference between the gains in height of the two groups is significant ($t = 2{\cdot}4$; $P =$ less than 0·02).

Puberty in obese girls. This study is based on the findings in the 47 girls who, at the last examination, were over the age of eight years. Growth of pubic hair was considered to have started when coarse pigmented hairs were present; fine non-pigmented hairs were ignored. Because in obese girls fat is deposited in the breast region, mammary development was considered to have started only when enlargement of the breasts was accompanied by enlargement of the nipples. As a standard for comparison the data of Hogben, Waterhouse, and Hogben (1948), based on the examination of 662 girls attending primary and secondary schools, were used. Figs. 7 to 10 compare the puberal development of the obese girls with the standard. Fig. 7 shows that some puberal mammary development was present in 50 per cent. of the nine-year-old obese girls, while the corresponding age for the standard is 11 years. Fig. 8 shows that 50 per cent. of the obese girls between the ages of nine and ten years showed growth of pubic hair, while the corresponding age for the standard is 11·8 years (11·3 years for girls above median height). Fig. 9 shows that 50 per cent. of the obese girls between 10½ and 12½ years of age showed the presence of axillary hair. The corresponding age for the standard is 13·2 years (12·6 years for the girls above median height). Fig. 10 shows that 50 per cent. of the obese girls between the ages of 12 and 13 years had started to menstruate. The corresponding age for the standard is 13·6 years (13 years for the girls above median height). It is concluded that puberty occurred earlier in the 47 obese girls than in the standard group. Probably the onset of menstruation is the most reliable criterion; according to this the onset of puberty occurred approximately one year in advance of that in normal girls of average height, but only six months in advance of that in normal girls of above-median height.

Puberty in obese boys. This study is based on the findings in the 30 boys who, at the last examination, were over the age of eight years. The criteria of puberal development used are the growth of pubic hair and axillary hair. Again the data of Hogben, Waterhouse, and Hogben (1948) provide the standard. They are based on the examination of 642 boys attending primary or secondary schools. Figs. 11 and 12 compare the puberal development with the standard. Fig. 11 shows that 50 per cent. of the obese boys between the ages of 11½ and 12½ years had pubic hair, while the corresponding age for the standard is 12·9 years (12·6 years for the boys above median height). Fig. 12 shows that 50 per cent. of the obese boys aged 13½ to 14 years had axillary hair, while the corresponding

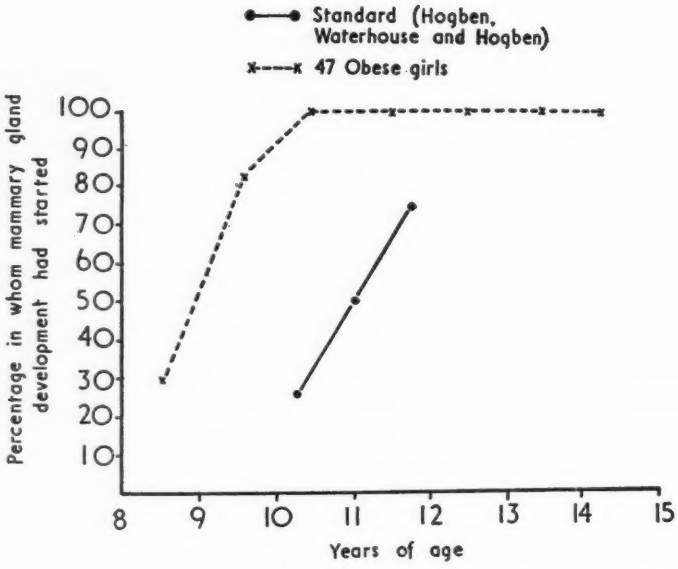

FIG. 7. Mammary gland development in obese girls.

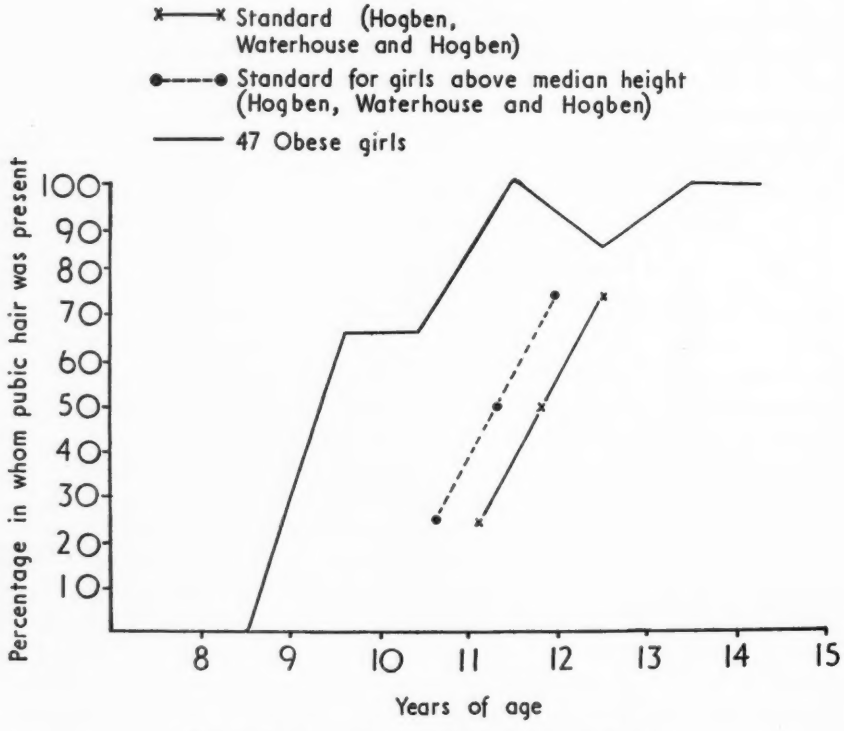

FIG. 8. Development of pubic hair in obese girls.

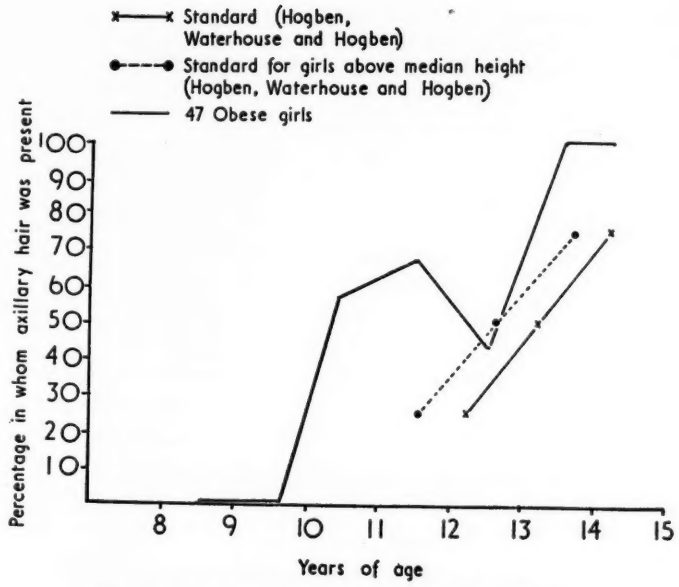

FIG. 9. Development of axillary hair in obese girls.

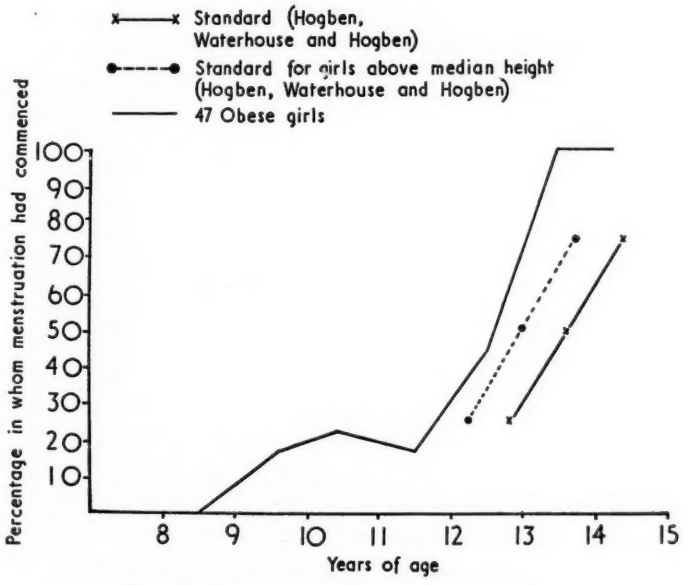

FIG. 10. Onset of menstruation in obese girls.

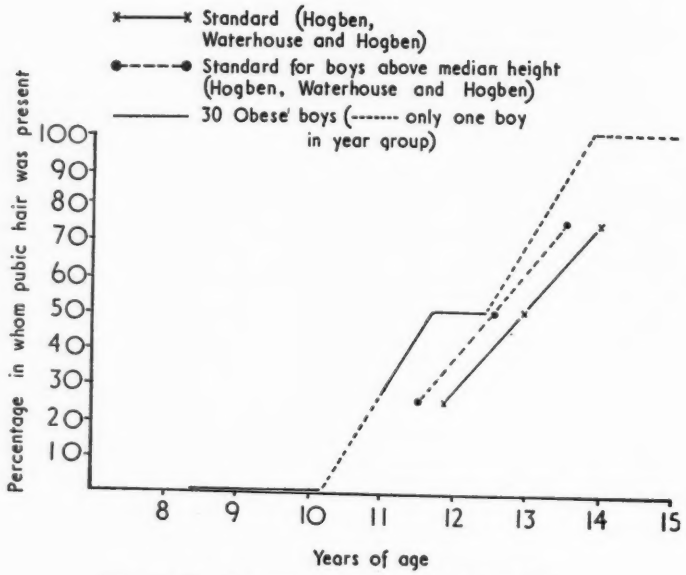

FIG. 11. Development of pubic hair in obese boys.

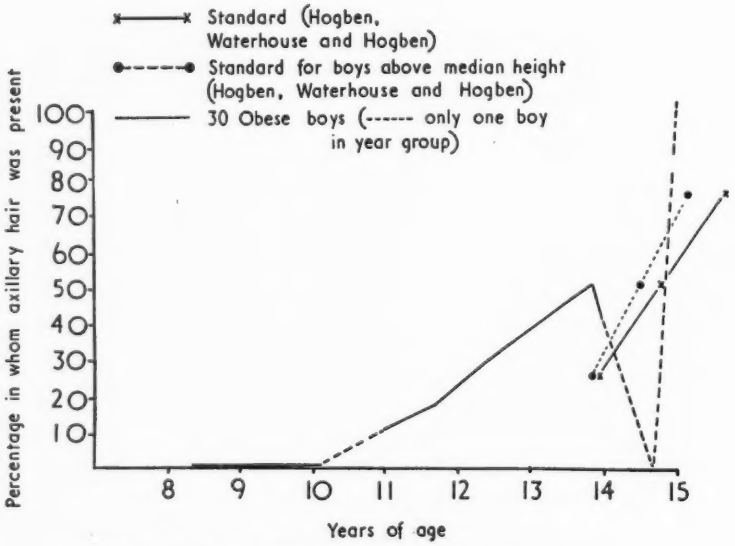

FIG. 12. Development of axillary hair in obese boys.

age for the standard is 14·8 years (14·5 years for the boys above median height). It is concluded that in the obese boys, as in the girls, puberty occurred approximately one year in advance of its time in normal boys of average height, but only six months in advance of that in normal boys of above-median height.

Significance of the Present Findings

Normal birth weight. This finding implies that childhood obesity is generally acquired, though it is possible that some children may have an abnormal appetite-regulating mechanism from birth, or even as an inherited condition.

Above-average height. Talbot and Sobel (1947) discussed the effect of nutrition on the growth of children. Undoubtedly undernutrition interferes with growth in height (Ellis, 1945; Butler, Ruffin, Sniffen, and Wickson, 1945; Daley, 1950; McCance and Widdowson, 1951). The effect of overeating is less certain. Bruch (1941) was unable to decide whether the increased rate of growth was the cause or the result of a large intake of food. Le Marquand and Tozer (1943) regarded the above-average height of obese children as the result of a pituitary abnormality, not simply of overeating. McCance (1953) found evidence that the rate of growth of children can be forced by overfeeding.

The present findings suggest that the excessive height is the result of a food intake in excess of requirements. If an abnormal growth-regulating mechanism were primary, and the excessive appetite secondary, a moderate reduction of the total calorie intake, with a reasonable intake of protein, vitamins, and minerals, and with the addition of the calories liberated from the dwindling fat deposits, should not lead to interference with growth in stature, but rather to sustained growth in height with a more rapid removal of the excessive fat deposits. If, however, a disturbance of the appetite-regulating mechanism were the cause of the excessive calorie intake, and if the increased rate of gain in height were the result of the excessive intake, one would expect a decreased rate of gain in height to result from a reduced calorie intake. Such a relationship between the rate of loss of weight—which is of course dependent on the caloric deficit—and failure to gain in height at the expected rate has been demonstrated in the present study. The fact that the height of the obese children was not significantly above that of children of the professional class provides further evidence that the obese child's height should be regarded not as outside the normal range, but merely as a result of a very adequate, or more than adequate, food intake. Fig. 6 shows that the close relationship between the rate of loss of weight and the failure to gain height at the expected rate applies to the children whose loss of weight did not exceed 3 per cent. of their standard weight per month. For the children who lost weight more quickly the relationship is less close. It is suggested that the limits had been reached beyond which further restriction of calorie intake would not interfere to a significantly greater extent with growth in height. Fig. 6 also shows that the children who failed to lose more than 1 per cent. of their standard weight per month grew in height above the expected rate; their calorie intake must still have been relatively high. The conclusion, that the children whose calorie intake remained high gained in height above the

expected rate, agrees with the finding that obese children tend to be above average height. Over the right-hand portion of the curve in Fig. 6 the close relationship between rate of loss (or gain) of weight and growth in height above the expected rate applies to the children who lost weight at a rate of 0·5 per cent. or more of their standard weight per month, but not to those who lost weight at a slower rate, or continued to gain weight. It is suggested that the limit was being reached beyond which a further increase in calorie intake would not lead to a significantly greater acceleration of gain in height. One can thus account for the fact that the obese children, whose food intake was presumably larger than that of children of the professional class, were not significantly taller than children of the professional class.

Early onset of puberty. It is known that undernutrition delays puberty (Butler, Ruffin, Sniffen, and Wickson, 1945; Ellis, 1945). Richey (1937) and Hogben, Waterhouse, and Hogben (1948) found that above-average weight and an above-average height tend to be associated with early puberty. The subject of height and puberty was studied systematically by Ellis (1946), who concluded that boys who enter puberty early are taller than their coevals who enter puberty late, and also that differences between the growth curves of the early- and late-maturing boys exist as far back as the sixth year of life. The present finding, that the obese children were above average height and entered puberty early, agrees with these observations. Ellis's (1946) height-for-age curves show that, at the age of 12 years, boys who were pubescent between 12 and 13 years were approximately 1·2 inches taller than boys destined to enter puberty a year later. This difference is in reasonably close agreement with the present finding that the obese boys aged 12 years were one inch above standard height (Fig. 2), and that their puberal development was one year in advance of the standard. It is probable that the height of obese children would not differ significantly from the height of non-obese children of the same age and sex who enter puberty a year ahead of the average.

Retardation of growth in height during period of rapid weight reduction. It is often stated that in the treatment of childhood obesity rapid reduction of weight is contra-indicated. The possibility that a low-calorie diet might interfere with growth in height has been quoted in support of this view (Ellis and Tallerman, 1934). It is possible from Fig. 6 to estimate to what extent growth in height is likely to be interfered with. Taking as an extreme example a child who is 100 per cent. above standard weight, one finds that, by losing weight at an average rate of 5 per cent. of the standard weight per month, this child would reach his or her standard weight in 20 months. If an expected yearly gain in height of three inches is assumed, the child would, during the period of weight reduction, grow four inches instead of five inches, that is 20 per cent. less than the expected gain. Usually the obesity will be less gross, the expected yearly gain in height will be less than three inches, and therefore the retardation of growth will amount to less than one inch. As most obese children are taller than the average, this slight interference with gain in height need not be regarded as important. In the unusual case of obesity in a child below average height it would appear

preferable to aim at a slower rate of weight reduction; a rate of 1 per cent. of the child's standard weight per month is unlikely to interfere with gain in height. In practice this means keeping the weight constant, and allowing the child to 'grow into the correct height for his weight'.

Though rapid weight reduction interferes with immediate growth in height, there is reason to believe that ultimately the height will be greater than it would have been, had the weight not been reduced or been reduced less rapidly. The obese child tends to enter puberty early and, as in the normal child, growth ceases within four to five years of the onset of puberty. Bruch (1941) suggested that some tall obese children finally have a stature below the average. If, during a period of weight reduction, growth in height is retarded, it is likely that the onset of puberty will be postponed to a more usual age, and therefore the total period of statural growth will be prolonged. Such postponement of puberty may be regarded as desirable. Sinclair (1953) stated that the maximum rate of growth is not the optimum, since overnourishment causes early maturity and might mean early death. McCance (1953), discussing growth and longevity, expressed similar views.

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Summary

The literature relating to the development of obese children is reviewed. The subjects of the present investigation were the first 100 children to attend an obesity clinic at the Children's Hospital, Birmingham.

The birth weights of the obese children were not above the average. The birth weights of the more obese children were not significantly higher than those of the less obese children.

The obese children were significantly taller than normal children from various social classes, but not significantly taller than children of the professional class.

During a period of rapid weight reduction the obese children showed less than the expected gain in height. The children who lost weight very slowly, or continued to gain weight, grew in height above the expected rate.

The onset of puberty was studied in 47 girls and 30 boys. In both sexes it occurred approximately one year in advance of the time of onset in normal children of average height, but only six months in advance of that in normal children of above-average height for their age.

Evidence is adduced in favour of the hypothesis that the above-average height, and the early age at the onset of puberty, of obese children are the result of a food intake above requirements.

The relatively slight retardation of growth during a period of rapid weight reduction need not be regarded as a disadvantage in the majority of obese children, who are in any case of above-average height.

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A CLINICO-PATHOLOGICAL STUDY OF DIABETIC GLOMERULOSCLEROSIS[1]

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With Plates 9 to 12

The present study is based on 120 consecutive cases of diabetes mellitus which came to post-mortem examination in the years 1951 to 1954 in the pathological service of Edinburgh University.

Glomerular Lesions

Since the original report by Kimmelstiel and Wilson (1936) there have been several detailed descriptions of the glomerular lesions. Within recent years a number of authors (Warren and LeCompte, 1952; Hall, 1952*a*; Robbins, Rogers, and Wollenman, 1952) have re-emphasized the nodular character of diabetic glomerulosclerosis for diagnostic purposes.

Nodular lesion. The typical lesion (Kimmelstiel-Wilson lesion or body) consists of a focal deposit of hyaline material in the centre of a glomerular lobule. This hyaline nodule is round or oval and has, characteristically, at its periphery one or more capillary loops separating it from Bowman's space. The smallest lesions which may be regarded as pathognomonic are at least 20 μ in diameter. In the mildest cases only one such minute nodule may be found in a section of kidney. An example of this early lesion is shown in Plate 9, Fig. 1. As the changes become more advanced the glomeruli usually contain more than one nodule. In severe cases, as in Plate 9, Fig. 2, the nodules may attain a diameter of over 100 μ, have often a laminated structure, and are present in almost every glomerulus. Even with these large deposits, the whole or part of a capillary loop can still be distinguished around the periphery of the hyaline mass. In some instances the capillary around a large nodule is grossly distended and of aneurysmal proportions (Plate 9, Fig. 3).

There is still considerable controversy over the histogenesis of the nodular lesion. Much of this controversy is due to a difference of opinion regarding the presence of an intercapillary connective tissue or space in the normal glomerular lobule. Kimmelstiel and Wilson (1936) considered that the hyaline material was intercapillary, and this view has been supported lately by McManus (1950). Allen (1941) and Bell (1950), however, denied the existence of an intercapillary tissue, and considered the nodular hyalinization to be intramural. Anderson

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(1954) suggested that the lesions are formed by plugging of glomerular capillaries by a protein coagulum deposited from the blood. We have studied a number of early cases of nodular glomerulosclerosis, using the periodic-acid-Schiff stain, and consider that the hyaline deposition is intercapillary.

For the purposes of recording the incidence and severity of diabetic glomerulosclerosis the nodular lesion alone has been considered. In the present series at least one section from each kidney was obtained in the majority of cases, but in a small proportion only one kidney section was available for study. Paraffin sections were cut at 4μ, and were stained with haemalum and eosin and with the periodic-acid-Schiff stain according to the method of McManus (1948). It was found that the periodic-acid-Schiff stain was of particular help in picking out small, scanty lesions, and for demonstrating capillary basement-membranes. Frozen sections were stained for fat in about 25 per cent. of the cases. The Kimmelstiel–Wilson lesion, body, or nodule is now considered to be specific for diabetes, though there are reports of cases showing such glomerular changes in which diabetes was never confirmed during life. We have encountered two such cases, which have not been included in the series. Both occurred in women. One of these women, aged 62 years, died a few hours after admission to hospital of a massive cerebral haemorrhage due to hypertension. Histological examination of the kidneys revealed typical nodular lesions in almost every glomerulus. The urine had not been examined, and her previous clinical history could not be obtained. The other, aged 65 years, died of a myocardial infarct after a few days in hospital. On two consecutive days she had no acetonuria, but small amounts of sugar, less than 0·5 gm. per 100 ml., were found in her urine. No further investigations were done, and no previous clinical records were available. A severe degree of diabetic glomerulosclerosis was found on histological examination. In both these cases the presence of diabetes could not be proved, though in the second the finding of glycosuria is highly suggestive. Two patients, included in the series, were not known at the time of post-mortem examination to have had diabetes, but on further inquiry were discovered to have been mild diabetics for several years. Each of these patients showed the typical nodular lesions histologically, and this finding prompted enquiries into their previous histories.

Diffuse glomerulosclerosis. Bell (1950) separated diabetic glomerulosclerosis into nodular and diffuse forms, and considered the diffuse type to be as characteristic of diabetes as the nodular variety. Diffuse glomerular hyalinization was encountered in some cases in the present series, and was the most striking feature in three (Cases 1, 2, and 3). Occasionally the hyaline deposit was focal in a glomerular lobule, but such nodules were small and tended to merge with the diffuse thickening of the tuft. The glomeruli themselves were enlarged, and the number of capillaries appeared to be increased. The outer capillary walls in contact with Bowman's space were usually thickened, partly owing to extension of hyaline material from the central parts of the glomerular lobules to the periphery. Many of the capillaries were reduced in calibre. A few were slightly dilated. These changes were best seen in Cases 2 and 3 (Plate 10, Figs. 5 and 6).

The diffuse glomerular hyalinization found in these three cases is, we think, the change described by Bell (1950). This lesion is similar to that found in a Type 2 nephritis, and differentiation between the two by the histological appearance of the glomeruli alone would be difficult if not impossible. The presence, however, of hyaline arteriolosclerosis of marked degree in all three cases would, we think, be of importance in excluding a Type 2 nephritis. Bell (1950) also considers this finding to be of prime importance in differentiating the two conditions.

Exudative lesion. The term exudative lesion was adopted by Hall (1952*a*) to indicate deposits in glomeruli of hyaline material which differs in staining properties and situation from the nodular or Kimmelstiel–Wilson lesions. The exudative lesion was originally described by Fahr (1942), and has been examined in some detail recently by Barrie, Aszkanazy, and Smith (1952), who referred to it as a 'fibrin cap', and by Koss (1952), who used the term 'hyaline-fibrinoid material'. The latter author found such lesions in other forms of nephropathy, but it was much more common and more severe in diabetes. Our experience is similar. The lesion is easily distinguished from the Kimmelstiel–Wilson bodies by haemalum and eosin stains. It is more brightly eosinophilic, often contains fatty vacuoles, and is situated at the periphery of the glomerulus in direct contact with Bowman's space (Plate 11, Fig. 9). The shape is variable, but most commonly crescentic. Lipoid material may be abundant (Plate 12, Fig. 10), and the lesion may consist mainly of a large droplet of fat surrounded by a thin rim of hyaline material. Such lesions may be found in large viable-looking tufts, but they are commonly seen in ischaemic glomeruli undergoing shrinkage. They may involve glomeruli with or without nodular glomerulosclerosis. Similar hyaline deposits may be found in Bowman's capsule and in the basement-membranes of the tubules. In the present series exudative lesions were found in about 25 per cent. of the cases of diabetic glomerulosclerosis, and occasionally in cases without a nodular lesion. They were most numerous in Cases 4, 5, 6, and 7.

The pathogenesis of these lesions and their exact situation in the glomeruli are still in doubt. They do not appear to develop into the nodular lesions of diabetic glomerulosclerosis, as no transitions between the two have been observed. They seem to us to arise in the basement-membrane of the outer wall of the glomerular capillary, and represent an accumulation of protein and fatty material which bulges both into Bowman's space and centrally into the capillary lumen, often obliterating the latter. Glomeruli containing several of these lesions therefore have many of their capillaries occluded, and the tufts become ischaemic, shrink, and become hyalinized. From our material we are unable to find any aetiological factor in the production of these lesions. All the kidneys in which they occurred have displayed moderate or severe arteriolosclerosis and arteriosclerosis, but these vascular changes may be found without exudative lesions. Large amounts of fatty material in many of them suggest a gross derangement in blood-lipoid, although we have no information on this point. They appear to represent an acute damage to the capillary wall, which results

in the escape of large amounts of albumin from the glomerular capillaries. If numerous they obliterate the capillary lumina, and eventually render the glomerulus functionless.

Capillary aneurysms occurred in a number of cases in the present series, and were conspicuous in Case 9 (Plate 9, Fig. 3). Allen (1941) considered such aneurysms important in the production of albuminuria. He suggested that they resulted from obstruction to the capillary outflow by the Kimmelstiel–Wilson bodies. Ashton (1950), by injection of Indian ink, beautifully demonstrated these glomerular aneurysms, and drew attention to the similarity of the changes in diabetic retinopathy and glomerulosclerosis. Anderson (1954) has found aneurysms in the glomeruli of diabetics, mainly in those which show no nodular lesions. He considered that nodular lesions develop by the plugging of these capillary dilatations with a protein coagulum from the blood. In our material we have found aneurysms most commonly associated with large and numerous nodular lesions, and consider that they are a relatively late phenomenon, which may well be due to obstruction of the capillary circulation by the large hyaline masses, as originally suggested by Allen (1941). Our findings do not suggest that diabetic retinopathy and glomerulosclerosis have a similar pathogenesis. In the retina capillary aneurysms are found early in the development of diabetic retinopathy, while in the kidney they occur relatively late.

Incidence

Of the 120 patients in the present series, 55 showed evidence of diabetic glomerulosclerosis, an incidence of 46 per cent. A review of previous reports shows a wide variation in the recorded incidence. Kimmelstiel and Porter (1948), from the reports published up to that time, considered that 17·1 per cent. was the average figure. Hall (1952*b*), however, in whose series 37·5 per cent. was recorded, pointed out that their methods of examining the figures were open to question. Most of the published reports have varied between 24·7 per cent. (Bell, 1950) and 44 per cent. (Goodof, 1945). In two series (Zins, 1949; Laipply, Eitzen, and Dutra, 1944) the incidence was considerably higher, 82 per cent. and 63·7 per cent. respectively, but in both instances the authors included diffuse glomerular hyalinization, and their figures are not therefore comparable. Our 55 cases were graded according to the number of glomeruli involved.

Grade I: less than 25 per cent. of the glomeruli involved.
Grade II: 26 to 50 per cent. ,, ,, ,,
Grade III: 51 to 75 per cent. ,, ,, ,,
Grade IV: over 75 per cent. ,, ,, ,,

Table I shows the distribution of the various grades of glomerulosclerosis. In the majority of instances it was found that in Grade I cases, where the

TABLE I

Distribution of Grades of Severity of Glomerulosclerosis in 55 Cases

Grade I	*Grade II*	*Grade III*	*Grade IV*
23 (41·8%)	9 (16·35%)	9 (16·35%)	14 (25·6%)

lesions were scanty, the nodules were small, while in the severe grades (III and IV) they were of moderate size or large, and usually multiple within individual glomeruli. In one case (Grade III), however, all the nodules seen were small (under 50μ) and apparently in the early stages of formation. As can be seen from Table I, severe grades of glomerulosclerosis (III and IV combined) formed roughly 40 per cent. of the total cases showing the lesion, giving an incidence in the whole series of 19·2 per cent. Diabetic glomerulosclerosis was therefore common, occurring in about half the diabetic patients coming to post-mortem examination, and was severe in about one-fifth of them.

Sex Incidence

All the earlier reports have emphasized the view that diabetic glomerulosclerosis is much more common in women than in men. Most of these communications, however, were based on small numbers of cases. Hall (1952*b*) analysed the large recorded series with regard to sex incidence, and found it varied, with one exception (Horn and Smetana, 1942; 3·8:1), from 1·2:1 to 1·75:1 of female to male patients. His own series showed a ratio of 1·4:1. Of the 120 patients in the present series 91 were female and 29 male. Forty-five of the female patients showed diabetic glomerulosclerosis, and 10 of the male patients; the incidence was therefore 49·5 per cent. in the women and 34·5 per cent. in the men. This gives a ratio of women to men of 1·43:1. These figures alone are not statistically significant, but when our figures are combined with those of other investigators there is a significant preponderance of female patients with diabetic glomerulosclerosis. It is interesting to note that Mann, Gardner, and Root (1949), studying the occurrence of the renal lesion in young diabetics, found it twice as common in male as in female patients, although the ratio of female to male patients in the hospital population generally was 3:2. Our series did not include a sufficient number of young diabetics for analysis in regard to sex incidence. The severe grades of glomerulosclerosis are generally considered to be much more frequently found in women than in men. Hall (1952*b*) had 14 cases of severe grade, 10 of which occurred in women. Platt and Davson (1950) and Gilliland (1951) reported similar findings. In the present series 19 of the 45 women with glomerulosclerosis, or 42·5 per cent., and four out of the 10 men, or 40 per cent., showed a severe degree of involvement (Grades III and IV combined). The ratio of female to male patients showing severe involvement is therefore almost 1:1. It appears, therefore, that though men are less prone to develop glomerulosclerosis than women, they are just as liable to develop severe grades of the lesion.

Duration of Diabetes

Table II shows the average duration of diabetes before death in patients both with and without glomerulosclerosis. Of those showing glomerulosclerosis there were 48 in whom the duration was known. In another four diagnosis had been made only a short time before death. There were 47 patients without the lesion regarding whom information was available as to the duration of diabetes. There

were also nine new patients in whom diabetes was diagnosed in the terminal illness. In all instances the duration is estimated from the date on which clinical diagnosis of diabetes was established. Most previous workers have indicated that duration does have an effect on the incidence and sometimes on the severity of glomerulosclerosis, the only dissenters being Laipply, Eitzen, and Dutra (1944), Rifkin, Parker, Polin, Berkman, and Spiro (1948), and Rifkin, Leiter,

TABLE II

Duration of Diabetes in Patients with and without Glomerulosclerosis

	With glomerulosclerosis (48 patients)	*Without glomerulosclerosis (47 patients)*
Average duration in all patients . . .	11·7 yrs.	7·3 yrs.
Average duration in patients under 50 years old	14·5 yrs.	12·2 yrs.
Average duration in patients over 50 years old.	10·8 yrs.	5·6 yrs.

TABLE III

Relation of Duration of Diabetes to Severity of Glomerulosclerosis

Duration of diabetes in years	*Severity of glomerulosclerosis*				*Total cases*
	Grade I	*Grade II*	*Grade III*	*Grade IV*	
0–5	6 (37·5%)	6 (37·5%)	1 (6·25%)	3 (18·75%)	16
6–10	5 (55·6%)	1 (11·1%)	1 (11·1%)	2 (22·2%)	9
11–15	6 (46%)	0	3 (23%)	4 (31%)	13
16–20	2 (20%)	1 (10%)	4 (40%)	3 (30%)	10
21 and over	1 (25%)	1 (25%)	0	2 (50%)	4

and Berkman (1952). Rifkin and his colleagues qualified their statement by suggesting that in some patients the diabetes may have been so mild that it was difficult to ascertain the exact date of onset of the disease. Mann, Gardner, and Root (1949) and Wilson, Root, and Marble (1951) have emphasized the significance of long duration in the development of renal complications in the young diabetic. It will be seen from Table II that the average duration of the diabetes in patients with glomerulosclerosis is significantly longer in those under 50 years old than in those over that age. Nevertheless, in patients of over 50 years who had glomerulosclerosis the average duration of diabetes was about twice as long as in those of over 50 years without the lesion. The significance of long duration of diabetes, in patients with glomerulosclerosis who died over the age of 50 years, is brought out by a study of all diabetics who died in this age group. In this series there were 23 patients who died over the age of 50 and whose diabetes had been present for more than 10 years. Of these patients 19 showed glomerulosclerosis, that is 82·6 per cent. Over the age of 60 there were 16 patients whose diabetes had been present for more than 10 years, and 14 of these patients showed glomerulosclerosis, that is 87·5 per cent. Over the age of 70, and with diabetes of more than 10 years' duration, there were seven patients, and all showed the lesion. The relation of the duration of diabetes to the severity of the glomerulosclerosis is shown in Table III. It appears that the longer the duration of the diabetes the more severe is the glomerular involvement, and the figures are statistically highly significant.

In eight cases of glomerulosclerosis diabetes was diagnosed less than a year before death. Seven of these patients were over 50 years old. The eighth was a woman aged 43 years, who was discovered to have diabetes only a few weeks before her death (Case 8 in the section dealing with the clinical syndrome). It is probable that in these eight patients the diabetes was so mild as to give rise to virtually no symptoms. The disease may well have been present for a considerable time before the diagnosis was made. It is not uncommon to have patients attending a diabetic out-patient clinic, with recently diagnosed diabetes, in whom diabetic retinopathy and neuropathy are already well established and the disease has presumably been present in a mild form for several years.

Age

The average age at death of patients with glomerulosclerosis was 63·3 years, and of patients without the lesion also 63·3 years. Of those who had glomerulosclerosis the youngest was 27 and the oldest 79 years old. Of the patients

TABLE IV

Distribution of the 120 Cases in regard to Age at Death

Age at death (years)	*0–9*	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*	*80 and over*
With glomerulosclerosis	..	..	1 (1·81%)	1 (1·81%)	7 (12·7%)	7 (12·7%)	23 (40·8%)	16 (29·6%)	.. ..
Without glomerulosclerosis	2 (3·15%)	..	1 (1·65%)	4 (6·3%)	8 (11·3%)	7 (10·8%)	23 (36%)	16 (24·6%)	4 (6·3%)

TABLE V

Incidence of Glomerulosclerosis among Patients Dying in Each Decade

Age at death (years)	*0–9*	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*	*80 and over*
Total number of cases	2	..	2	5	15	14	46	32	4
With glomerulosclerosis	..	..	1	1	7	7	23	16	..
Percentage	..	..	50	20	46·7	50	50	50	0

showing glomerulosclerosis 83·6 per cent. were over 50 years old; but 81·6 per cent. of the group without the lesion were also over 50. Diabetes is undoubtedly more common in the elderly. The distribution of the 120 cases is analysed according to age at death in Table IV. The earlier reports stressed the prevalence of the lesion in the older age groups, and in the present series the largest number of cases was found in the seventh decade. Reference to Table V, however, reveals that the incidence of glomerulosclerosis in younger age groups is just as high as in the seventh and eighth decades when expressed as a percentage of the total deaths. The number of cases in the age groups 20 to 29 and 30 to 39 is too small for analysis, but it is significant that in the fifth decade almost half of the patients with diabetes had developed the lesion.

Severity of Diabetes

In the present series there were 86 patients about whom satisfactory details of treatment were available. These were divided into five groups according to their insulin requirements.

Group I: diet alone.
Group II: diet and up to 20 units of insulin daily.
Group III: diet and 21 to 40 units ,, ,,
Group IV: diet and 41 to 60 units ,, ,,
Group V: diet and over 60 units ,, ,,

The distribution of the 86 cases according to these grades of severity of diabetes is shown in Table VI. The majority of cases of glomerulosclerosis

TABLE VI

Severity of Diabetes in 86 Cases

	Group I	*Group II*	*Group III*	*Group IV*	*Group V*
Total number of cases . . .	29	34	12	5	6
44 patients with glomerulosclerosis	13	19	7	4	1
42 patients without glomerulosclerosis	16	15	5	1	5

(72·8 per cent.) are found in Groups I and II, that is in patients with mild diabetes. But 73·8 per cent. of patients without the lesion are also in those two groups. In patients with more severe diabetes the relative incidence of glomerulosclerosis is still high. It is over 50 per cent. in Group III, and reaches almost the same figure in Groups IV and V combined. Patients with diabetes of any degree of severity can, and often do, develop glomerulosclerosis. This finding is in accord with the recent observations of Hall (1952*b*) and Platt and Davson (1950). Mann, Gardner, and Root (1949) and Wilson, Root, and Marble (1951) have drawn attention to the fact that glomerulosclerosis is a common complication in young patients with severe diabetes.

Zubrod, Eversole, and Dana (1951) reported a decrease in insulin requirements in patients with severe glomerulosclerosis. They suggested that in such patients the diabetes may appear mild and be difficult to detect. We have not observed this phenomenon in the present series. Two possible alternative explanations for this apparent amelioration of the diabetes are offered. First, patients with severe renal involvement usually have a raised renal threshold for sugar, and if the diabetes is being controlled only by testing the urine their insulin requirements will appear to have fallen, because less insulin is needed to obtain a sugar-free urine. Secondly, they are often sufficiently ill to develop anorexia, and even to those who are in reasonably good health a low-sodium diet is distasteful, and their calorie intake falls.

Control of Diabetes

In earlier papers dealing with the subject the effect of control of the diabetes upon the incidence of diabetic glomerulosclerosis was either ignored or else considered to be of little importance. Studies carried out upon young diabetics indicate that poor control predisposes to the development of glomerulosclerosis (Wilson, Root, and Marble, 1951; Mann, Gardner, and Root, 1949). Dunlop (1954) has recently shown, in a clinical study of patients with diabetes of at

least 15 years' duration, that the over-all incidence of complications is higher in poorly controlled patients. In the investigation of the particular problem a great many difficulties are encountered. In the first place it is not always possible to obtain sufficient information about the control of a given case, especially if the diabetes has been present for a long time. In the present series only those cases in which adequate information was available have been analysed. In the second place it is by no means easy, in retrospect, to assess the control

TABLE VII

Control	*Total number of cases*	*With glomerulosclerosis*	*Without glomerulosclerosis*
Good	10	2 (20%)	8 (80%)
Moderate . . .	31	12 (38·5%)	19 (61·5%)
Poor	37	21 (57%)	16 (43%)

TABLE VIII

	Percentage with good control	*Percentage with moderate control*	*Percentage with poor control*
35 patients with glomerulosclerosis .	5·7	34·3	60
43 patients without glomerulosclerosis .	19·1	45·2	35·7

of any given patient. Short of carrying out frequent estimations of the blood-sugar over a long period, it is impossible to obtain an accurate assessment of the control of the diabetes, and obviously this is not a practical proposition. In patients in whom the renal threshold for sugar is raised the amount of glycosuria gives very little indication of the blood-sugar level, and many patients suffering from diabetic glomerulosclerosis have a high renal threshold for sugar. Symptoms such as thirst and polyuria are dependent not upon the level of the blood-sugar but upon the degree of glycosuria, and are consequently unreliable indications of diabetic control in the presence of renal damage. The same objection applies to the use of variations in body-weight as a guide to control. In the present series we have divided the cases into three groups, showing good, moderate, and poor control respectively, according to the following criteria:

Good. Those patients who had been regular in attending a diabetic out-patient department, and had never been in diabetic coma or had any serious degree of ketosis. The urine had usually been free of sugar, or had shown only a trace of sugar.

Moderate. Those whose attendance at a diabetic out-patient department was regular, and in whom no serious degree of ketosis occurred, but whose urine generally contained 'sugar+' to 'sugar++'.

Poor. This group contained those patients who had defaulted from the out-patient clinics, those who had been admitted in diabetic coma, and those whose urine had shown ketone bodies from time to time when they reported at the out-patient department.

The figures in Table VII are statistically significant (χ^2 for trend = 5·24 for one degree of freedom). It appears from Tables VII and VIII that the poorly

controlled patient is more likely than the well controlled patient to develop glomerulosclerosis. In the well controlled group only two patients (20 per cent.) showed evidence of the lesion, and in both instances it was of relatively mild degree (Grade II). In the group in which control had been poor, on the other hand, 57 per cent. of the patients showed the typical changes in the glomeruli. Of these almost half had severe involvement (Grades III and IV), and of those who have been placed in Grades I and II on account of the paucity of nodular lesions four showed either severe diffuse glomerular hyalinization or numerous exudative lesions. It seems, therefore, that poor control is at least a contributory factor in the development of diabetic glomerulosclerosis.

As we have already shown, the duration of diabetes is another important causal factor, and it is of interest to note that, in the poorly controlled group, the average duration of diabetes in patients with glomerulosclerosis was 14·7 years, whereas in patients without the lesion it was 7·8 years. In this series, however, there are two patients who had been poorly controlled for a long period of time and whose kidneys showed none of the characteristic pathological changes *post mortem*. In both these cases degenerative changes throughout the arterial tree were minimal. It is difficult to explain how these patients failed to develop renal complications. It appears that there must be other factors operating about which we know very little.

The Clinical Syndrome associated with Diabetic Glomerulosclerosis

When Kimmelstiel and Wilson (1936) described the distinctive glomerular changes, they found them fairly constantly associated with diabetes mellitus, oedema of nephrotic type, and gross albuminuria. Hypertension was frequently present, in many cases associated with renal decompensation. We consider that the most important components of this syndrome, apart from diabetes, are albuminuria and nephrotic oedema. Judged by these criteria there were 11 patients in the series who presented the fully developed clinical syndrome. Incidentally all except one (Case 8) were hypertensive, and eight showed evidence of renal impairment. Table IX gives the details of these 11 cases. The histological changes in the kidneys, however, varied, though they fell roughly into three groups.

Cases 1, 2, and 3 showed similar glomerular changes. The most striking feature was the paucity of nodular lesions, and all three cases were classified as Grade I glomerulosclerosis. They all, however, displayed diffuse hyaline deposition throughout the tufts. This change was conspicuous in Cases 2 and 3 (Plate 10, Figs. 5 and 6) and less striking in Case 1 (Plate 10, Fig. 4). Additional features were, first, the presence of exudative lesions in all three cases. These lesions were scanty in Case 3, and moderately numerous, that is present in about 20 per cent. of glomeruli, in Cases 1 and 2. Secondly, severe atheromatous narrowing (Plate 11, Fig. 7) of several of the interlobar branches of the renal arteries was present in Case 2, with the commencement of widespread glomerular atrophy (Plate 11, Fig. 8). This was reflected clinically in the moderate nitrogen retention found in this case.

Table IX

Analysis of 11 Cases of the Fully Developed Clinical Syndrome

Case number	Sex	Age at onset of diabetes (years)	Age at death	Duration of diabetes (years)	Severity of diabetes (Group)	Control of diabetes	Grade of glomerulo-sclerosis	Albuminuria	Oedema	Plasma-proteins (gm./100 ml.) (A. albumin G. globulin)	Blood-pressure	Renal function*	Duration of diabetes (years) at onset of glomerulo-sclerosis	Duration of diabetes (years) thereafter	Cause of death
1	M	23	32	9	V	Poor	I	1 gm./litre	+	A. 3·03 G. 1·68 } 4·71	230/115	BUN 13	7	2	Hypoglycaemic coma
2	F	20	41	21	III	Moderate	I	3½ gm./litre	++	A. 3·54 G. 2·31 } 5·85	170/100	NPN 51	17½	3½	Coronary thrombosis
3	F	13	27	14	IV	Poor	I	+	+	..	180/100	..	12½	1½	Diabetic coma
4	M	25	42	17	III	Moderate	IV	12 gm./litre	+++	A. 3·4 G. 2·97 } 6·37	210/105	BUN 67	15	2	Uraemia
5	F	35	46	12	II	Poor	IV	5 gm./litre	+	A. 3·35 G. 2·02 } 5·37	160/110	BUN 88	9	3	Miliary tuberculosis
6	F	?65	71	?6	I	Poor	IV	8 gm./litre	+	A. 3·05 G. 3·06 } 6·11	150/110	NPN 113	?	6	Uraemia
7	M	30	47	17	III	Poor	..	+++	+++	A. 2·4 G. 2·6 } 5·0	230/130	Blood-urea 316	15	2	Uraemia
8	F	..	43	..	..	..	IV	8 gm./litre	+	..	185/85	BUN 254	..	..	Uraemia
9	F	58	65	7	IV	Poor	IV	2 gm./litre	+	A. 3·4 G. 1·8 } 5·2	180/100	..	3	4	Coronary thrombosis
10	M	54	68	14	I	Moderate	IV	+++	+	A. 3·6 G. 2·1 } 5·7	185/100	BUN 70	10	4	Coronary thrombosis
11	M	33	46	13	II	Poor	III	+	+	A. 3·73 G. 2·68 } 6·41	140/100	NPN 54	12	1	Coronary thrombosis

* BUN = Blood urea nitrogen (mg. per 100 ml.). NPN = Non-protein nitrogen (mg. per 100 ml.).

The next five cases (Cases 4, 5, 6, 7, and 8) have been grouped together because they were characterized clinically by very massive albuminuria, varying from 5 gm. per litre (Case 5) to 12 gm. per litre (Case 4). We have no figures for Case 7, but this patient showed a heavy and persistent albuminuria (+++) for several months. In four of these patients (Cases 4, 5, 6, and 7) there were numerous exudative lesions in the renal glomeruli. Cases 4, 5, and 6 were essentially similar in renal histology. All showed Grade IV nodular glomerulosclerosis and severe arteriolosclerosis. Exudative lesions were present in about half the glomeruli, many of which were undergoing ischaemic atrophy (Plate 12, Fig. 11). Arteriosclerosis of the interlobular and arcuate arteries was also moderately severe, but atheroma of the interlobar branches, though present, was not severe. Case 5 was complicated by a tuberculous pyelonephritis. Case 7 showed the most severe involvement by exudative lesions, and is remarkable in that no nodular lesions were found. Many tufts were completely ischaemic and hyalinized, while most of the remainder contained masses of exudative lesions (Plate 12, Fig. 12). In addition an active chronic pyelonephritis was present. Atheroma of the interlobar arteries was present, but the lumina were not greatly narrowed. Case 8 differed from the other four cases in that diabetes was diagnosed only a few weeks before the patient's death. For some years she had been treated for periodic oedema of the ankles, episodes which were thought to be due to cardiac failure. In hospital she showed no evidence of cardiac failure, and the oedema was considered to be nephrotic. No previous records of examination of the urine were available, but in her last illness there was albuminuria of the order of 8 gm. per litre. The histological detail of the kidneys was very poor because of severe post-mortem autolysis. There was also an extensive acute pyelonephritis. Grade IV lesions of diabetic glomerulosclerosis were present, but no exudative lesions could be made out. Apart from Case 8, therefore, there appears to be a correlation between the exudative lesions in the glomeruli and the presence of large amounts of albumin in the urine. It should also be noted that exudative lesions were present in moderate numbers in Case 2, and in this patient 3½ gm. of albumin per litre were recorded in the urine. Koss (1952) found that 12 of the 13 patients about whom he had the relevant information had severe albuminuria in association with exudative lesions.

The histological changes in the kidneys in Cases 9, 10, and 11 were similar, but different in degree. All showed a severe degree of glomerulosclerosis. Exudative lesions were present in small numbers in Case 9, but were very scanty in Cases 10 and 11. Capillary aneurysms were present in all three cases, and were prominent in Case 9 (Plate 9, Fig. 3). They were less numerous and smaller in Cases 10 and 11. In the latter two cases they were no more prominent than those occurring in several other cases with severe glomerulosclerosis, but in Case 9 they were larger and more numerous than in any other case in the series.

Of the remaining patients who had glomerulosclerosis there were 29 about whom we have adequate clinical information. We considered that persistent

TABLE X

Analysis of Seven Cases in which Glomerulosclerosis was Strongly Suspected because of Persistent Albuminuria

Case number	*Sex*	*Age at onset of diabetes (years)*	*Age at death (years)*	*Duration of diabetes (years)*	*Severity of diabetes (Group)*	*Control of diabetes*	*Grade of glomerulo-sclerosis*	*Albumin-uria*	*Oedema*	*Blood-pressure*	*Duration of diabetes (years) at onset of glomerulo-sclerosis*	*Duration of diabetes (years) thereafter*	*Cause of death*	*Remarks*
12	F	61	70	9	I	Poor	I	+++	+ Cardiac	210/120	9	Few weeks	Coronary thrombosis	Scanty nodular lesions. Slight diffuse glomerulosclerosis Exudative lesions +
13	M	75	78	3	II	Moderate	III	½ gm./ litre	+ Cardiac	190/70	2	1	Coronary thrombosis	..
14	F	50	58	8	IV	Poor	III	+	+ Cardiac	195/110	7½	6 months	Cerebral thrombosis	..
15	F	36	49	13	IV	Poor	IV	+	Nil	170/94	11	2	Pulmonary tuberculosis	Small number of exudative lesions. Aneurysms
16	F	26	52	26	II	Poor	IV	+	Nil	145/90	26	Few weeks	Coronary thrombosis	..
17	F	?60	63	?3	IV	..	I	+	Nil	215/115	?	3	Broncho-pneumonia	Nodular lesions, very scanty. No other glomerular changes
18	F	44	53	9	I	Poor	I	+	Nil	210/120	7	2	Massive pulmonary embolism	Diffuse glomerulosclerosis +. Nodular lesions, scanty

albuminuria of the order of one plus (+) or more, in the absence of any other cause and particularly of urinary infection, would be the best indication of glomerulosclerosis. There were seven patients who fulfilled these criteria, and the details are given in Table X. It will be seen that only four of these patients showed a severe degree of glomerular involvement, that is Grade III or IV, and in three it was classed as Grade I. The other 22 patients had shown no evidence during life of glomerulosclerosis, as judged by the above degree of

TABLE XI

	Number of patients	*Glomerulosclerosis*				*Without glomerulosclerosis*
		Grade I	*Grade II*	*Grade III*	*Grade IV*	
Classical clinical syndrome .	11	3	..	1	6	1 (Case 7)
Glomerulosclerosis strongly suspected clinically	10	3	..	2	2	3
Glomerulosclerosis present but not suspected clinically . .	22	11	4	4	3	..

albuminuria. Seven had severe glomerulosclerosis (Grades III and IV) and in the other 15 it was mild (Grades I and II). It is noteworthy that all these seven patients with severe glomerulosclerosis were over 60 years old, except one aged 57 years.

Judged by the criterion of persistent albuminuria there were three further patients who clinically were suspected to have glomerulosclerosis, but at autopsy failed to show it. The first, a man aged 56, had diabetes for 26 years. He developed severe albuminuria and nephrotic oedema, but gave a previous history of acute nephritis, and *post mortem* the changes typical of subacute glomerulonephritis (Ellis Type 1), with numerous epithelial crescents, were found. The second patient, a woman aged 61, had had persistent albuminuria ($\frac{1}{2}$ to 1 gm. per litre) since the discovery of the diabetes three years before her death. Histologically the kidneys showed severe arteriolosclerosis, but the glomeruli were normal. The third, a man aged 52, had diabetes for five years and albuminuria for several months before his death. At autopsy there was atheroma of the renal arteries and their branches, but only mild arteriolosclerosis. The glomeruli were normal, and there was no severe ischaemic atrophy.

Table XI summarizes the above findings.

Discussion of the Clinico-pathological Correlation of Diabetic Glomerulosclerosis

After the original description of the lesion by Kimmelstiel and Wilson in 1936, several reports confirmed the association between the glomerular lesion and the development of a clinical syndrome of oedema, albuminuria, hypertension, and renal impairment (Anson, 1938; Derow, Altschule, and Schlesinger, 1939;

Newburger and Peters, 1939; Simon, 1940; Herbut, 1941; Porter and Walker, 1941). Siegal and Allen (1941) thought there was a definite relationship between the degree of glomerular involvement and the development of the clinical syndrome. Nevertheless, of their 10 patients who had a severe degree of glomerulosclerosis only three showed the complete renal syndrome, and of 18 patients who showed the syndrome partially or completely, four, including one case of amyloidosis, did not have diabetic glomerulosclerosis. In the last 10 years when larger series of cases have been examined, it has been reported that the nephrotic syndrome is uncommon in patients who show diabetic glomerulosclerosis *post mortem* (Henderson, Spraue, and Wagener, 1947; Laipply, Eitzen, and Dutra, 1944). From a review of the literature Kimmelstiel and Porter (1948) considered that it was present in less than 10 per cent. of cases of glomerulosclerosis. Platt and Davson (1950) stated that there are cases in which oedema does not occur. Rogers and Robbins (1952) considered that no clear-cut syndrome exists, and that a diabetic patient not having the anatomical lesion may clinically present the so-called classical features of glomerulosclerosis, while on the other hand many, if not most, patients who have glomerulosclerosis do not show those clinical features. They thought, however, that the condition is more often missed than wrongly diagnosed. Adams (1947) on the other hand reported five patients, all young diabetics, who developed the classical clinical syndrome and died in uraemia. *Post mortem* none showed nodular glomerulosclerosis, though diffuse glomerular hyalinization was present.

Reference to Table XI will show that in the present series there is little correlation between the severity of nodular glomerulosclerosis and the accuracy of diagnosis of the condition during life. We agree with Rogers and Robbins (1952) that the condition is more often missed clinically than wrongly diagnosed. Of the 11 patients presenting the classical clinical syndrome it is important to note (Table IX) that eight were under 50 years old. We have found that the more clinically obvious examples of diabetic glomerulosclerosis occur in the younger age groups. Mann, Gardner, and Root (1949) described the development and course of the clinical syndrome in young diabetics. The first sign is albuminuria, which becomes more severe, and nephrotic oedema, often intermittent, then appears. The blood-pressure rises, and later renal failure supervenes, and death in uraemia. This was the course of events in the majority of our 11 patients, though several died of other diabetic complications before renal insufficiency became severe. We have been impressed by the absence of any correlation between the levels of the plasma-proteins and the appearance of oedema in several of these patients. Mann, Gardner, and Root (1949) reported similar experiences, and found that hypoproteinaemia was a late phenomenon in many such cases. Four of our 11 patients died in uraemia, and another four showed evidence of renal impairment. Hall (1952*a*) drew attention to the importance of severe atheroma of the small renal arteries in the association of diabetes with uraemia in such patients. In the present series there was only one instance (Case 2) in which atheroma of the branches of the renal arteries was severe and appeared to be of importance in producing renal cortical

destruction. In most of the other cases it was present but not of remarkable degree. We have, however, since this series was completed, encountered three patients with diabetic glomerulosclerosis who died in uraemia and in whom severe renal atheroma with widespread cortical atrophy was found *post mortem*.

Of the seven patients in whom the clinical diagnosis was made from the presence of persistent albuminuria alone, four died under the age of 60, while of the seven with severe grades of glomerulosclerosis unsuspected during life six were over 60. It appears therefore that the diagnosis of diabetic glomerulosclerosis during life is much more commonly made in patients under 60 years old. Over that age patients usually die of other diabetic complications, without giving any clinical evidence of glomerular involvement. Spühler (1944) has suggested dividing the clinical picture of diabetic glomerulosclerosis into three types. In young diabetics the nephrotic syndrome is the initial feature, with elevation of blood-pressure and symptoms and signs of nephrosclerosis later. In middle-aged diabetics the vascular and nephrotic syndromes develop simultaneously. Elderly diabetics with glomerulosclerosis usually do not show the nephrotic syndrome, and signs of nephrosclerosis are predominant. Our experiences in the present study have been similar.

Hypertension is an almost constant feature of the clinical syndrome, as reference to Tables X and IX will show. It is, however, a common complication of diabetes, though present slightly more often in patients with glomerulosclerosis than in those without the lesion. In the present series 82·5 per cent. of the patients with glomerulosclerosis had diastolic hypertension, as opposed to 60 per cent. of those without glomerulosclerosis. Gilliland (1951) considered retinopathy and neuropathy to be essential components of the fully developed syndrome, and Ashton (1951) found that all the patients he examined who had glomerulosclerosis had also diabetic retinopathy. We have not sufficient information in the present series about the incidence of retinopathy, though in one patient with Grade III glomerulosclerosis diabetic retinopathy was not observed during life. It must be admitted, however, that this patient was not examined by an ophthalmologist, and the retinae were not examined *post mortem*. Neuropathy was found in patients with glomerulosclerosis almost twice as frequently as in those without the lesion (68·5 per cent. and 37·5 per cent. respectively). Neuropathy does not appear to be an essential part of the clinical syndrome, and serves only as confirmatory evidence in individual cases.

Causes of Death

It will be seen from Table XII that the most important cause of death in both groups is coronary artery disease. It is of interest that in this series the incidence of uraemia was almost the same in patients who had as in those who did not have glomerulosclerosis. In view of the fact that it has been suggested that ketosis is very uncommon in patients with diabetic glomerulosclerosis, it is noteworthy that in the present series the incidence of diabetic coma as a cause of death is not significantly lower among patients who showed the lesion. The relatively high number of deaths due to pulmonary embolism is accounted for

by the fact that about one-sixth of the patients in this series died in surgical wards after undergoing operations.

TABLE XII

Analysis of Causes of Death in 120 Patients

	With glomerulosclerosis	*Without glomerulosclerosis*
Coronary artery disease .	20	18
Hypertensive cardiac failure	1	4
Diabetic coma . . .	8	10
Pneumonia . . .	6	4
Uraemia	4	4
Cerebral thrombosis . .	2	3
Tuberculosis . . .	3	2
Malignancy . . .	4	6
Miscellaneous . . .	6	8
Pulmonary embolism . .	1	6
	55	65

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Summary and Conclusions

1. A clinico-pathological study of diabetic glomerulosclerosis was made in 120 consecutive cases of diabetes mellitus coming to post-mortem examination within a three-year period.

2. The lesion was found in 46 per cent. of cases, being slightly more common in women than in men.

3. Diabetic glomerulosclerosis is considerably more common in poorly controlled diabetes. Poor control is therefore one factor in the production of the lesion.

4. The average duration of diabetes in patients with glomerulosclerosis was 11·7 years, and in those without the lesion 7·3 years. The duration of diabetes is an important causal factor in the production of the lesion, particularly in the younger age group.

5. The severity of glomerulosclerosis is related to the duration of the diabetes.

6. Most cases of glomerulosclerosis are found in the seventh and eighth decades, but the majority of cases of diabetes, with or without renal lesions, occur in these age groups. In most decades, however, the incidence of the lesion is approximately 50 per cent.

7. The incidence of glomerulosclerosis does not bear any relation to the severity of the diabetes.

8. There were 11 patients with the fully developed clinical syndrome of albuminuria and nephrotic oedema. There was no constant histological pattern in the renal glomeruli in these cases.

9. Massive albuminuria appears to be related to the presence of exudative lesions in the glomeruli.

10. Most patients with mild glomerulosclerosis do not show clinical evidence of its presence, and seven cases of severe glomerulosclerosis were not clinically obvious.

11. Young diabetic patients with glomerulosclerosis show clinical evidence of the lesion more commonly than elderly diabetics.

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FIG. 1. Small nodular lesion. Note the ring of intact capillaries around it (periodic-acid-Schiff and haematoxylin, ×430)

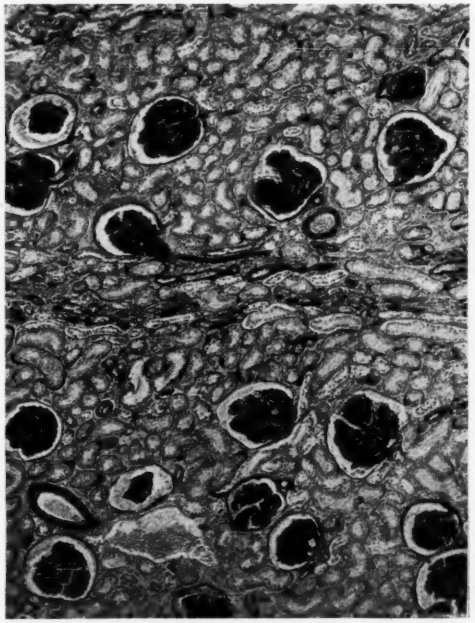

FIG. 2. Case 9. Severe diabetic glomerulosclerosis. Every glomerulus in the field contains at least one nodular lesion. Many of these bodies are large (periodic-acid-Schiff and haematoxylin, ×40)

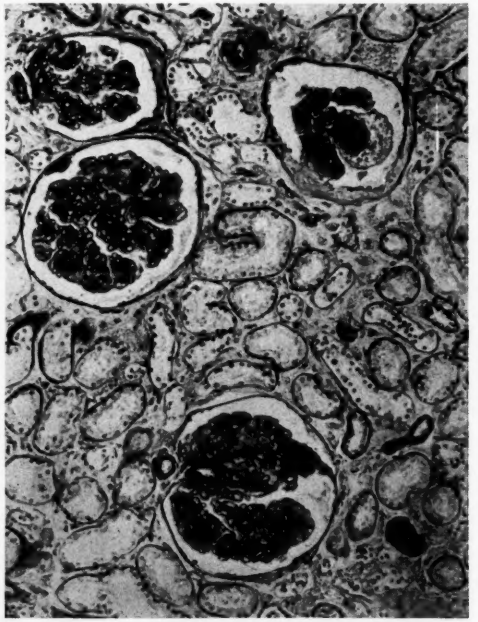

FIG. 3. Case 9. Capillary aneurysms. A grossly distended capillary encircling a large nodular lesion is seen in the glomerulus (top right). A smaller aneurysm is present in the glomerulus below (periodic-acid-Schiff and haematoxylin, ×100)

FIG. 4. Case 1. Moderate diffuse glomerulosclerosis. A small exudative lesion is present (top left). Note the severe afferent and efferent arteriolosclerosis (periodic-acid-Schiff and haematoxylin, ×430)

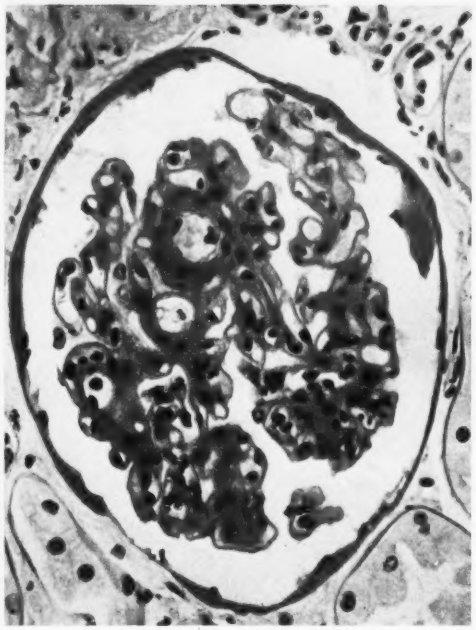

FIG. 5. Case 2. Severe diffuse glomerulosclerosis. Many of the capillaries are narrowed and their basement membranes thickened (periodic-acid-Schiff and haematoxylin, ×430)

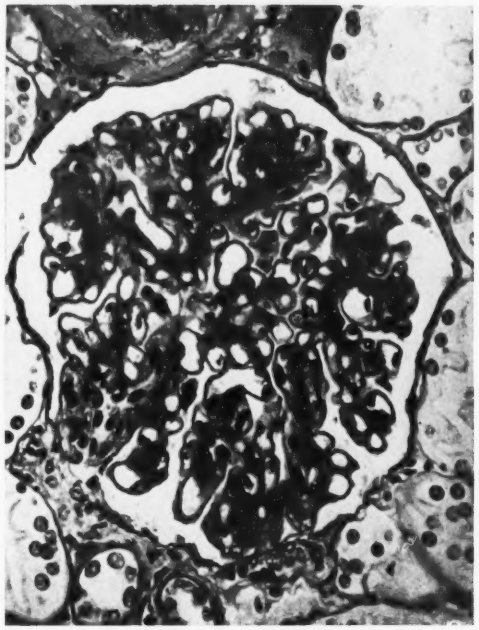

FIG. 6. Case 3. Severe diffuse glomerulosclerosis. Similar lesion to Case 2 (periodic-acid-Schiff and haematoxylin, ×430)

FIG. 7. Case 2. Severe atheroma of an interlobar artery (haematoxylin and eosin, ×40)

FIG. 8. Case 2. More than half of the glomeruli show varying degrees of ischaemic atrophy due to severe atheroma of the interlobar arteries (periodic-acid-Schiff and haematoxylin, ×40)

FIG. 9. Exudative lesion. Several of these lesions are present in the lower half of the glomerulus. Note that the hyaline material is in direct contact with Bowman's space. The vacuolation is due to fat. The remainder of the glomerulus shows diffuse hyalinization and obliteration of most of the capillary lumina (haematoxylin and eosin, ×430)

FIG. 10. Case 7. Frozen section stained with Scharlach R to show large amounts of fatty material in exudative lesions. The fat appears jet black (×100)

FIG. 11. Case 4. Severe nodular glomerulosclerosis plus numerous exudative lesions (periodic-acid-Schiff and haematoxylin, ×100)

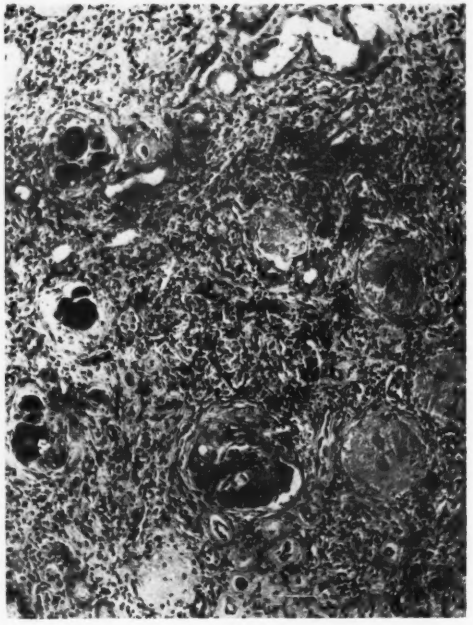

FIG. 12. Case 7. Numerous exudative lesions are present in the glomeruli in the left half of the field. The tufts in the right half are completely ischaemic (haematoxylin and eosin, ×100)

616.329-009.7

OBSERVATIONS ON DISTENSION OF THE LOWER END OF THE OESOPHAGUS[1]

By J. H. BAYLIS, R. KAUNTZE, and J. R. TROUNCE

(From the Departments of Medicine and Pharmacology, Guy's Hospital)

With Plate 13

Although it has for long been recognized that distension of the lower end of the oesophagus produces pain, and the relation of such pain to activity in the oesophagus has been analysed in some detail (Payne and Poulton, 1923–4, 1927; di Core, 1929; Polland and Bloomfield, 1931), the realization that pain somewhat similar to that of cardiac ischaemia occurs in such conditions as spasm or diverticulum of the oesophagus, with or without oesophagitis (Edeiken, 1939; Guyot and Blum, 1949), and in hiatus hernia (Jones and Chapman, 1942) is more recent. Schrager and Ivy (1928) had previously maintained that reflexes arising from the oesophagus, diaphragm, stomach, or gall-bladder in health or disease could affect the coronary circulation. Guyot and Blum (1949) wrote that when an atypical angina pectoris occurred without radiation of pain to the arms, and food and swallowing precipitated the pain, an oesophageal origin should be suspected, and that radiology and endoscopy were too rarely practised in such circumstances. Unfortunately a lax cardia and the sliding type of hiatus hernia can be shown with suitable technique in about five per cent. of all barium-meal examinations, with or without symptoms (Hodson, 1954). Furthermore von Bergmann (1932) noted that dilatation at or just above the cardia was a frequent radiological finding in patients with anginal pain (*das epiphrenale Syndrom*). It is important, therefore, to have some other and reliable criterion to distinguish between a cardiac and an oesophageal origin of thoracic pain. The literature shows disagreement on certain points in the differential diagnosis. There are four main ways in which cardiac pain might be distinguished from pain arising in the oesophagus:

1. The character, distribution, and duration of the pain.
2. The relationship of the pain to effort.
3. The relief of the pain by nitrites or other drugs.
4. The electrocardiogram.

The objects of the present paper are to review briefly the value of these criteria in the diagnosis, and by experiment and observation on the oesophagus to attempt to clarify those points which are obscure. The second criterion, namely the relationship of the pain to effort, although historically important, was not readily amenable to experimental study.

[1] Received October 9, 1954.

The character of oesophageal pain is considered by most observers to resemble closely that of cardiac pain. Edeiken (1939) reported a patient with both spasm of the cardia and angina pectoris, and noted the similarity between the two types of pain; he also quoted Morrison (1939), who found that the pain produced by experimental distension of the oesophagus, regardless of the site, was similar to that of angina pectoris. Polland and Bloomfield (1931) listed the characteristics of pain in patients subjected to distension of the oesophagus; although a wide range of descriptions was used, some of them, such as 'contraction' or 'painful pressing', were equally applicable to ischaemic cardiac pain. Evans (1952), in his St. Cyres Lecture, again emphasized the resemblance of oesophageal pain to that arising from the heart. Polland and Bloomfield (1931), in an experimental study of the effects of oesophageal distension in 39 subjects, found that the site of pain bore no relationship to the position of the balloon. It occurred especially at the suprasternal notch or at the xiphoid process; less often it spread over the front of the chest, or to the back, and rarely to the neck or face. Moersch and Miller (1943) reported that the pain may be more widespread, and may be referred to the ear, face, neck, shoulders, and even down the arm to the hand. The consensus of opinion, therefore, is that the nature and distribution of the pain arising from the oesophagus are similar to those found in cardiac ischaemia, and thus not useful in distinguishing these conditions.

The effect of nitrites on cardiac pain is well known, but their effect on pain arising from the oesophagus is not so clear-cut. Evans (1952) found that some of his patients with oesophageal arrhythmia were relieved by nitrites. Wolferth and Edeiken (1942) considered atropine more effective than nitrites in relieving oesophageal pain; a similar view was expressed by Harrison (1945). Douthwaite (1943) found full, though temporary, relaxation with amyl nitrite in achalasia, and with glyceryl trinitrate a less complete but more lasting effect. Jones and Chapman (1942) noted that relief of the pain in a hiatus hernia was sometimes given by atropine or nitroglycerine, but not invariably. Although octyl nitrite will also allow emptying of the oesophagus in some cases of achalasia, pain is not as a rule a leading symptom in this condition.

The electrocardiographic changes in cardiac ischaemia are now clearly defined, and with the introduction of the effort test it is possible to show significant depression of the RS–T segment in 95 per cent. of sufferers, provided they are exercised to the point of dyspnoea or pain (Wood, McGregor, Magidson, and Whitaker, 1950). This method should therefore provide a ready means of distinguishing between cardiac and oesophageal pain. Morrison, however, (1939) is quoted as having found transient electrocardiographic changes after oesophageal distension in normal subjects (Edeiken, 1939). Morrison and Swalm (1940, Case 4) reported that distension of balloons in the oesophagus and stomach in a patient with hypertensive heart disease led to increased ventricular irritability, as shown by extrasystoles, and also noted R–T changes under pressures of 25 to 40 mm. Hg. Examination of their published records shows no control tracing, and although the RS–T segment and the degree of

T inversion vary a little from record to record (all of lead I), so does the amplitude of the QRS complex, and the possibility of positional change is difficult to exclude; in addition the T-wave inversion is presumably from left ventricular strain. Weiss and Ferris (1934) reported a patient in whom distension of an oesophageal diverticulum produced a Stokes-Adams attack with complete auriculo-ventricular block and syncope. Such attacks could be abolished by atropine, and were considered to be of reflex origin, from irritation of the vagus nerve-endings in the diverticulum. The authors also noted that distension of the oesophagus in normal subjects, and in those with overactivity of the carotid sinus, failed to produce fainting or any change in cardiac rhythm. Gilbert, Fenn, and LeRoy (1940) reported that distension of a dog's stomach, under anaesthesia or not, produced coronary vasoconstriction which was abolished by atropine. They also found that patients with angina of effort breathing 10 per cent. oxygen developed pain more quickly after meals, and that this reduced pain-time could be counteracted by atropine. Julian (1953) described ischaemic changes in the electrocardiogram of a patient with an epiphrenic oesophageal diverticulum; the changes disappeared when the oesophageal sack was emptied, and he postulated some oesophageal-cardiac reflex as their cause. Harrison (1945), however, in discussing the differential diagnosis of cardiac and oesophageal pain, considered that the electrocardiogram was of great value, provided that undue emphasis was not placed on borderline findings. There are two sources of error in attributing changes in the electrocardiogram after oesophageal distension to reflex cardiac ischaemia. First, changes in the electrical axis of the heart produced by enlargement of the oesophagus may alter the electrocardiogram and lead to a false diagnosis of cardiac ischaemia. Secondly, patients in whom the oesophagus is distended from one cause or another are no more immune from coronary artery disease than the rest of the population, and isolated reports of ischaemic changes found in these patients should be received with reserve, particularly if tachycardia is concurrently induced.

It appears therefore from a review of published reports that pain originating in the oesophagus, whether produced experimentally by distension or arising from oesophageal disease, bears a close resemblance both in character and distribution to cardiac pain, although more precise analysis of the nature of the pain might reveal differences. There is disagreement both as to the result of oesophageal disease on the electrocardiogram and as to the effects of atropine and nitrites on oesophageal activity and pain. For these reasons the effects of distension of the lower end of the oesophagus have been investigated.

Method

The oesophagus was distended by a rubber bag attached to a soft rubber catheter. The bag was made of two layers of condom rubber. A little barium sulphate solution was introduced between the inner and outer layers, so that its outline could be seen on fluoroscopy. The inner bag contained about 0·5 ml. of mercury, which weighted the bag and thus made it easier to swallow. The

bag was passed down the oesophagus until it lay just above the cardia (Plate 13, Fig. 5). The rubber catheter was attached to a small mercury manometer with a light writing-arm floating on the surface of the mercury; the pressure changes were recorded on a revolving drum as required. The system was filled with air, and inflation of the bag was by means of a sphygmomanometer

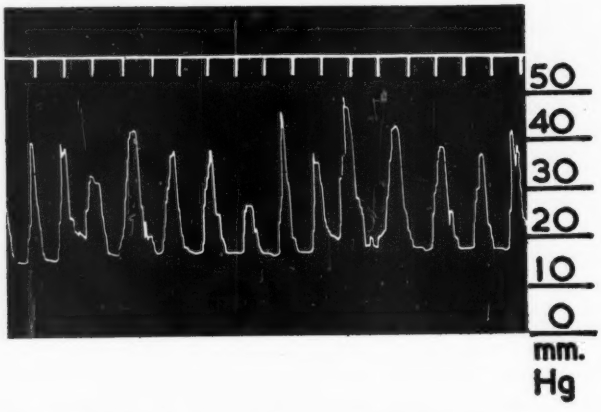

FIG. 1. Tracing of changes in intra-oesophageal pressure due to contractions following distension of the bag in the lower oesophagus. Time marking at 10-second intervals.

bulb. The position and changes in shape of the bag were observed by fluoroscopy throughout the experiment, the patient remaining semi-recumbent. The electrocardiogram was recorded on a direct-writing machine, standardized so that 1 millivolt equalled 1 cm. deflection. Eight normal young men, three men suffering from coronary artery disease, with typical electrocardiographic changes on effort (flat depression of the RS–T segments), and one man with achalasia of the cardia were studied. In 11 subjects the sensations produced by distension of the bag and the effect on the electrocardiogram were recorded. In three of the normal subjects the results of amyl nitrite and atropine on the sensation produced by distension of the bag, and on the oesophageal contractions as recorded by the pressure manometer, were studied. The patient with achalasia of the cardia was observed as regards the effect on the electrocardiogram of gross distension of the oesophagus. In this instance the oesophagus was distended with barium emulsion, and not with a bag.

Results

Oesophageal activity. In all subjects inflation of the bag in the lower end of the oesophagus was associated with spontaneous and rhythmic oesophageal contractions. These contractions tended to drive the bag and tube further down the oesophagus, and were therefore presumably of a peristaltic nature. The frequency of contraction and rise in pressure were variable, but a typical

tracing is shown in Fig. 1. This form of oesophageal activity has already been fully described (Payne and Poulton, 1923–4, 1927).

Pain. Some degree of pain was produced in all subjects by distension of the lower oesophagus with a mean pressure of about 30 mm. Hg, which inflated the bag to about 4.5 cm. diameter. In two subjects this amounted to little more than discomfort, and higher pressure still failed to produce marked pain.

The Effects of Oesophageal Distension on the Patient and his Electrocardiogram

			Pain				Intra-oesophageal pressure (mm. Hg)	Effect on electrocardiogram
Case number	Sex	Age (years)	Character	Situation	Points of reference	Constant or fluctuating		
Normal subjects:								
1	M	22	Aching	Deep substernal	None	Wave of pain with contraction	30/40	None
2	M	23	Dull	Lower substernal	None	Wave of pain with contraction	12/35	None
3	M	22	Dull	Deep substernal	Back	Wave of pain with contraction	15/40	None
4	M	24	Distension	High epigastric and lower substernal	None	Continuous	20/40	None
5	M	32	Distension	Lower substernal	None	Wave of pain with contraction	15/25	None
6	M	23	Discomfort	Lower substernal	None	Only with contraction	20/45	None
7	M	21	Distension	Lower substernal	Throat	Wave of pain with contraction	25/46	None
8	M	22	Distension	Lower substernal	None	Only with contraction	18/45	None
Subjects with coronary artery disease:								
9	M	51	Fullness and burning	Lower substernal	None	Wave of pain with contraction	35/100	None
10	M	53	Distension	Lower and upper substernal	None	Continuous	20/50	None
11	M	40	Distension	Lower substernal and upper epigastric	None	Continuous	37/50	None

The character of the pain is summarized in the table. It was usually described as a feeling of distension or fullness—never of constriction—and sometimes as aching and spasmodic. The three subjects who had true cardiac pain stated that the two types of pain were quite different, although they were unable to define clearly the differential points. The pain was usually felt behind the lower sternum and localized to this region, though in one case it was referred to the back, and in another was also felt at the back of the throat. In all but three subjects the pain became worse with oesophageal contraction. Between contractions it was only a mild discomfort, but with a rise in oesophageal pressure it became a real pain. It was noticed that the pain was related not only to the rise in pressure recorded by the manometer, but to the actual contraction of the oesophagus as seen on fluoroscopy.

The electrocardiogram. Electrocardiograms, consisting of the standard leads, lead III in full inspiration, the unipolar limb leads, and precordial leads, were recorded from all patients before the bag was swallowed, with the bag in situ

but not inflated, and with the bag inflated and producing pain. In no case was there any significant change in the record, even when the pain was quite severe. The three patients with coronary artery disease were then exercised to the production of dyspnoea or pain, and the electrocardiograms repeated;

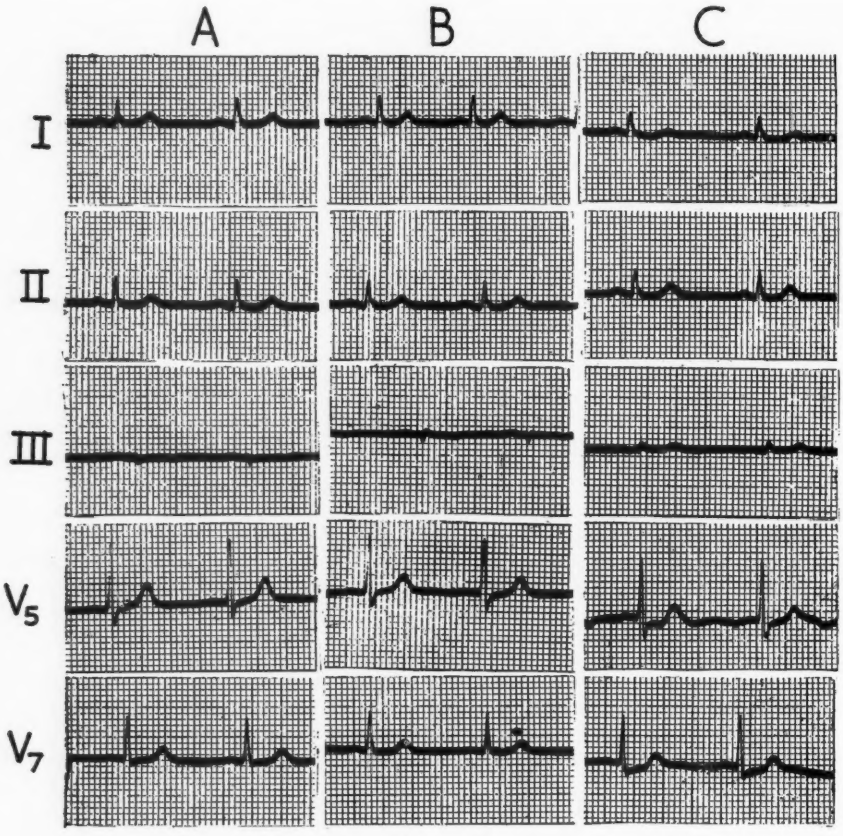

FIG. 2. Electrocardiogram of a subject with coronary artery disease (A) at rest, (B) during distension of the bag in the oesophagus to a pressure of 20/50 mm. Hg, which provoked pain without cardiographic change, and (C) three minutes after exercise consisting of 20 steps, 30 inches high, showing ischaemic changes in leads V_5 and V_7.

in each case they showed changes typical of ischaemia. One such record is shown in Fig. 2. It was not possible, therefore, even in subjects with very limited coronary reserve, to find any evidence that distension of the lower oesophagus caused cardiac ischaemia, by reflex narrowing of the coronary arteries, or any other electrocardiographic change. Gross enlargement of the oesophagus, such as may occur in achalasia of the cardia, may produce changes in the electrocardiogram, not by any effect on the coronary circulation or heart muscle, but merely by displacing the heart. This fact is well illustrated

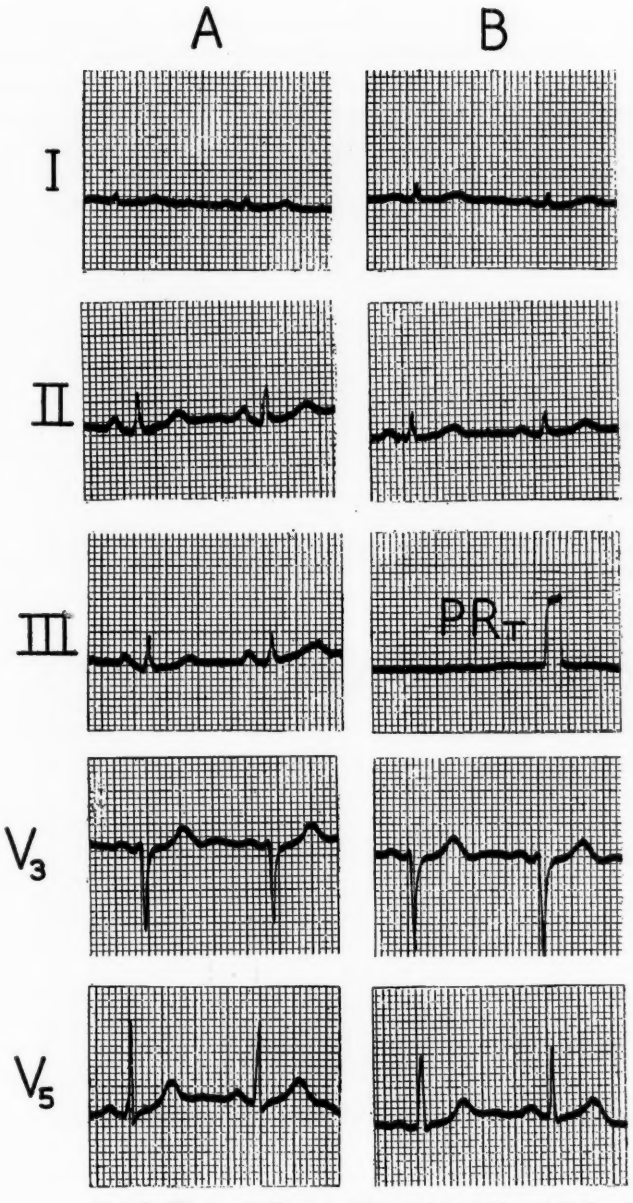

FIG. 3. Electrocardiogram of a patient with achalasia of the cardia, (A) with oesophagus empty, (B) with oesophagus distended by 400 ml. dilute barium solution, showing changes in lead III, from the electrical axis becoming transverse. After successful operation on the oesophagus such changes no longer occurred.

in Fig. 3, which shows the cardiographic changes produced by distending the oesophagus in a patient who had severe achalasia of the cardia. These appear-

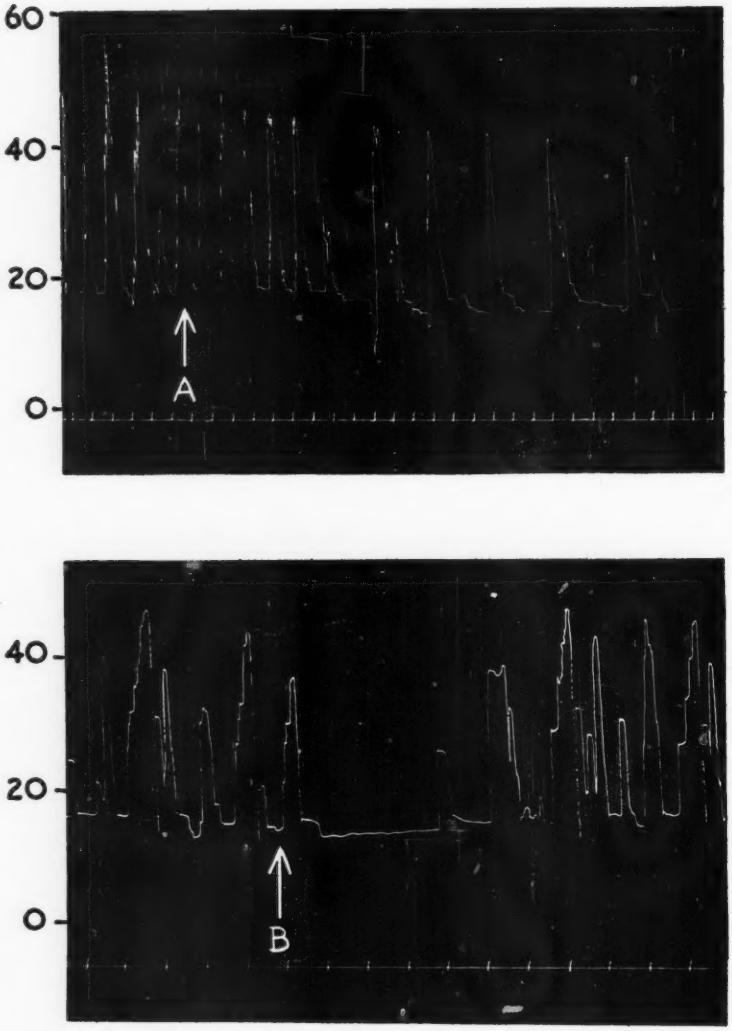

FIG. 4. Tracings showing changes in intra-oesophageal pressure due to contractions following distension of the bag in the lower oesophagus before and after atropine and amyl nitrite. A: intravenous injection of 1·3 mg. of atropine; B: inhalation of amyl nitrite. Time marking at 10-second intervals; pressure in mm. Hg.

ances are quite distinct from the effects of anoxia or chemical change on the myocardium.

The effect of drugs. The effects of atropine and amyl nitrite on the pain and

activity provoked by oesophageal distension were investigated in three of the normal subjects (Fig. 4). Atropine 1·3 mg. given intravenously in all three subjects caused a decrease in the frequency of oesophageal contraction provoked by a constant stimulus. There was no change in the amplitude of contraction as previously recorded, but the contraction and relaxation of the muscle were slower. The decrease in frequency of contraction made the exacerbation of pain less frequent, but when it occurred the slower contraction provoked pain quite as severe as the exacerbations before the drug was injected. The inhalation of amyl nitrite temporarily inhibited all oesophageal activity in two of the three subjects investigated. While there were no oesophageal contractions pain was relieved. In the third subject it appeared to have no effect on the severity of the pain or on oesophageal activity.

Discussion

In discussing the above findings we would emphasize the fact that oesophageal distension, with its attendant pain, is not necessarily the mechanism which obtains in oesophageal disease. Our findings, however, suggest that the pain produced by oesophageal distension is usually associated with powerful oesophageal contractions, the type of activity which is also associated with pain in the group of conditions called variously oesophageal arrhythmia, oesophageal spasm, or 'corkscrew' oesophagus. The nature of the pain provoked by our experiments appeared to those suffering from coronary artery disease to be quite distinct from ischaemic cardiac pain, being rather a sense of distension or fullness than a feeling of oppression or constriction. Although this difference may appear plain to those suffering from both types of pain, such a difference may be difficult to elicit from a patient who is only suffering from one type of pain, especially as many find the exact description of pain difficult. Medical students, however, in whom oesophageal pain was produced thought such pain different from the description of anginal pain. When severe, the pain would rapidly reach a climax and equally rapidly abate, in about 10 to 30 seconds, a time relationship alien to angina pectoris. The distribution of oesophageal pain appears to resemble closely that of cardiac pain, and to be of no help in the diagnosis, though we did not encounter radiation of pain to the arm or jaw. The absence of radiation of pain in our patients may be due to the retention of the bag in the lower oesophagus throughout, as confirmed by fluoroscopy. Among the associated symptoms were salivation, which occurred apparently just before or with the onset of pain, slight nausea, and the desire to vomit when the pain reached its height. The effect of amyl nitrite on oesophageal activity and pain was variable, and that of atropine was slight. It is notoriously difficult to assess the effect of drugs on pain, and the use of this point in the diagnosis is probably open to the pitfalls of suggestion.

Although there seems little doubt that in certain subjects distension of the oesophagus has produced changes in cardiac rhythm, perhaps mediated by the vagus, no such arrhythmia occurred in our patients. Anrep and Segall

(1926) were able to produce vasomotor changes in the coronary arteries of dogs by stimulation of vagal and sympathetic nerve-endings in the lower oesophagus or stomach, and their findings as regards the stomach were later confirmed by Gilbert, Fenn, and LeRoy (1940). As it was considered that the vagus predominated in the tonic control of the coronary arteries, the postulate of coronary spasm from irritation of the vagus was a logical inference. Our experiments, however, have not shown that it is possible in man by oesophageal distension to cause reflex narrowing of the coronary arteries, with electrocardiographic evidence of myocardial ischaemia. The electrocardiogram therefore appears to offer the most useful method of distinguishing between cardiac and oesophageal pain. This opinion is supported by the extensive follow-up studies of Evans (1952), who found that, whereas there were 184 deaths from cardiac infarction in 1,000 patients with chest pain and an abnormal cardiogram, in 332 patients with chest pain and a normal resting cardiogram there were 14 deaths, in 13 of which the causes were outside the heart.

Summary

The pain produced by distension of a balloon in the lower oesophagus has been studied in eight normal subjects and in three subjects with coronary artery disease.

The nature and distribution of the pain, and its response to atropine and amyl nitrite, are discussed.

The electrocardiographic records taken before and during distension of the oesophagus are analysed.

It is concluded that oesophageal pain, as produced by distension of the lowest third, differs from that of cardiac ischaemia in its character, its fluctuating nature, the speed of its precipitation and abolition, and the absence of electrocardiographic change. Distension of the lower oesophagus in patients with presumptive coronary atheroma, in whom left ventricular leads after effort showed typical ischaemia, had no effect on the cardiogram. Distension of the lower oesophagus in achalasic dilation produced the cardiographic changes of axis shift alone. Atropine given intravenously slightly diminished the frequency of contraction to a constant simulus, and had no analgesic effect. Amyl nitrite temporarily inhibited contraction and thereby abolished pain. Finally, in our opinion the electrocardiogram offers the most reliable means of distinguishing between oesophageal and cardiac pain.

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FIG. 5. Right anterior oblique X-ray of the chest, showing the bag in position inflated to 30 mm. Hg

616.24–007.63–08

CARBON DIOXIDE NARCOSIS IN EMPHYSEMA[1]

By E. KEITH WESTLAKE, THOMAS SIMPSON, AND MICHAEL KAYE

(From Chase Farm Hospital, Enfield, Middlesex, and the Postgraduate Medical School of London)

'My reader will not wonder that, having ascertained the superior goodness of dephlogisticated air by mice living in it. . . . I should have the curiosity to taste it myself. . . . Who can tell but that in time this pure air may become a fashionable article in luxury. Hitherto, only two mice and myself have had the privilege of breathing it.'—*Experiments and Observations on Different Kinds of Air.* Joseph Priestley, London, 1775.

ALTHOUGH oxygen has been used for over 50 years for the relief of anoxaemia in pneumonia and similar respiratory diseases, reports of untoward effects attributable to its administration have appeared only in recent years. In 1937 Barach, one of the pioneers of oxygen therapy, recorded that 'oxygen treated patients may develop a state of stupor, with irrationality when aroused, lasting from one to five days', and again in 1941 he wrote: 'A profound disturbance of mental functioning may take place in patients suffering from longstanding arterial anoxaemia after inhalation of 50 per cent. oxygen, invariably temporary, but occasionally lasting over a week. . . . In most cases a slowly deepening stupor occurs which may progress to a comatose state with periods of irrationality when awakened. In some patients lassitude and mental depression take place accompanied by severe headache.' Barach originally ascribed these symptoms to a sudden change of cerebral oxygen tension, but there is now general agreement that mental symptoms appearing during oxygen therapy are usually due to intoxication by carbon dioxide (Donald, 1949, 1953; Comroe, Bahnson, and Coates, 1950; Hickam, Sieker, Pryor, and Ryan, 1952; Bickerman and Beck, 1952; Westlake, 1953; Lovejoy, Yu, Nye, Joos, and Simpson, 1954). The present paper reviews the clinical and biochemical findings in 16 cases of carbon dioxide narcosis studied between November 1950 and April 1954.

Patients Investigated and Methods

Fourteen patients were suffering from chronic bronchitis and emphysema. As judged by hypertrophy of the right ventricle on fluoroscopy, 11 of them had developed cor pulmonale. Two patients were asthmatic subjects. The acute respiratory disturbance necessitating emergency admission to hospital was lobar pneumonia in one patient, bronchopneumonia in five patients, bronchitis or bronchiolitis in eight, and status asthmaticus in two. Nine patients were in congestive cardiac failure (Table I). On admission to hospital a sample of

[1] Received November 3, 1954.

TABLE I

Carbon Dioxide Narcosis in Emphysema

Case number	Age (years)	Sex	Diagnosis*	Acute respiratory condition	Congestive cardiac failure	Blood gases: Before oxygen therapy — O_2 saturation (%)	pH	Plasma CO_2 (vols. %)	pCO_2 (mm. Hg)	During oxygen therapy — O_2 saturation (%)	pH	Plasma CO_2 (vols. %)	pCO_2 (mm. Hg)	On recovery from acute respiratory condition — O_2 saturation (%)	pH	Plasma CO_2 (vols. %)	pCO_2 (mm. Hg)	Mental state and neurological signs during oxygen therapy
1	51	F	E:CB:CP	Bronchiolitis	Yes	45·0	..	91·0	..	100·0	..	109·0	..	84·0	7·33	86·3	72	Coma, dilated pupils, and muscular twitching after 20 min.
2	60	M	E:CB:CP	Bronchitis	Yes	61·5	7·29	96·5	86	90·0	7·24	108·0	109	89·5	7·41	78·1	54	Stuporose after 24 hrs.; disorientation and hallucinations when aroused
3	53	M	E:CB:AS	Bronchiolitis	No	35·7	..	69·5	..	100·0	..	106·0	..	91·5	7·40	64·6	46	Stupor alternating with hypomania for first 55 hrs.
4	53	M	E:CB:HTHD	Bronchitis	No	65·5	..	72·8	..	..	..	83·5	..	92·6	7·38	63·4	47	Semicoma, myoclonic jerking
5	62	M	E:CB:CP	Bronchitis	No	64·0	7·26	73·8	72	..	7·13	82·8	105	..	..	..	..	Semicoma, profuse sweating, twitching of arms
										..	7·26	96·9	93	..	..	..	..	Drowsy but rational
										94·0	7·12	93·8	121	..	..	..	..	Semicoma
6	55	F	A:AI	Status asthmaticus	No	..	..	..	..	96·0	7·16	72·3	86	95·6	7·43	64·6	42	Semicoma
7	67	M	E:CB:CP:HT	Bronchopneumonia	Yes	65·4	7·38	69·5	52	..	7·22	84·5	89	..	..	..	..	Drowsy, disorientated, and euphoric after 12 hrs.
										..	7·13	101·0	129	..	..	..	..	Semicomatose after 65 hrs.
										..	7·22	134·0	140	..	..	..	..	Semicomatose after 83 hrs.
8	52	M	E:CB:CP	Lobar pneumonia	Yes	53·4	7·33	79·6	66	97·5	7·07	87·6	102	88·8	7·40	61·1	43	Coma, imperceptible respirations, gallop rhythm, hypotension after 3 hrs.
9	58	F	A:TB	Status asthmaticus	No	..	..	..	..	92·0	6·88	91·0	193	..	..	..	..	Coma. Died 28 hrs. later
10	63	M	E:CB	Bronchitis	No	63·9	7·39	75·6	55	..	7·25	80·2	80	95·9	7·40	52·6	37	Drowsy, confused, and apathetic after 8 hrs.
11	64	M	E:CB:CP:KS	Bronchitis	Yes	81·3	7·29	83·4	75	..	7·16	97·1	115	..	..	..	..	Semicomatose after 2 days
12	58	F	E:CB:CP:A	Bronchitis	No	53·1	7·28	82·5	76	97·6	6·83	80·0	187	..	..	..	..	Comatose after 24 hrs.
13	46	M	E:CB:CP	Bronchopneumonia	Yes	..	..	..	..	86·4	7·29	102·0	92	86·1	7·37	83·6	64	Drowsy and confused with bilateral papilloedema after 36 hrs.
14	64	M	E:CB:CP:HT	Bronchopneumonia	Yes	42·1	7·31	90·0	77	..	7·03	95·0	155	..	..	..	..	Comatose after 24 hrs.
										..	7·13	93·0	118	..	..	..	..	Stuporose after 40 hrs. Died on the following day
15	76	M	E:CB:CP	Bronchopneumonia	Yes	81·4	7·34	64·4	52	..	7·24	85·0	85	..	..	..	..	Drowsy and complaining of headache
16	49	M	E:CB:CP	Bronchopneumonia	Yes	..	7·20	73·4	80	..	7·16	80·7	96	..	..	..	..	Stuporose after 4 hrs.
										..	7·07	88·7	127	..	..	..	..	Comatose after 12 hrs.

* E = emphysema. CB = chronic bronchitis. CP = cor pulmonale. AS = ankylosing spondylitis. HT = hypertension. HTHD = hypertensive heart disease. A = asthma. AI = syphilitic aortic incompetence. TB = tuberculosis. KS = kyphoscoliosis.

arterial blood was taken from the brachial artery under local analgesia, and further samples at intervals during oxygen therapy. Ventilation was recorded with a Benedict-Roth spirometer, rubber mouthpiece, and nose-clip. When measurements were made during oxygen therapy, air in the spirometer bell was replaced by pure oxygen. Minute-volume of ventilation was calculated from the spirographic tracing by summation of individual breaths. Samples of arterial

TABLE II

Respiratory Function Tests

Case number	*Vital capacity (ml.)*	*RC/TLC*	*Maximum breathing capacity (l./min.)*	*Mixing efficiency* (%)*	*Poorly ventilated space* (ml.)*	*$RRCO_2$**
1	1,460	71	19	85	1,550	0.333
2	1,910	66	55	40	1,390	..
3	2,250	45	38	80	480	0·838
4	2,890	59	33	49	1,900	0·964
5	1,320	74	..	..	..	..
10	2,820	58	51	56	1,200	..
11	1,400	55	19	100	0	0·231
12	1,750	57	..	..	1,400	..
13	2,620	56	34	56	1,360	0·716
Normal values	..	<45	>100 in males >80 >80 in females		<500 ml.	0·9–4·5

RC = residual lung capacity; TLC = total lung capacity; $RRCO_2$ = respiratory response to inhalation of CO_2 (in litres per mm. rise in carbon dioxide tension).

* As determined by the method described by Prime and Westlake (1954).

blood were analysed for oxygen content, oxygen saturation, and total carbon dioxide content of the plasma by the method of Van Slyke and Neill (1924). Blood pH was measured with a Cambridge pH-meter in a closed glass electrode at room temperature. Correction of the observed pH to the patient's body temperature at the time of taking the arterial sample was made by Rosenthal's factor (1948). Arterial carbon dioxide tension (pCO_2) was calculated from the total carbon dioxide content of the plasma and the pH by using the Henderson-Hasselbalch equation. Oxygen was administered by tent, giving an inspired-oxygen concentration of between 40 and 50 per cent. During oxygen therapy any alteration in the patient's mental state was recorded, and subsequently correlated with changes in arterial pH and pCO_2. The cerebrospinal fluid pressure was measured in a glass manometer calibrated up to 700 mm. On recovery from the acute respiratory disturbance the arterial blood analyses were repeated. The maximum breathing capacity was measured with the patient breathing into a Douglas bag for 20 seconds as rapidly and deeply as possible. The expired air was then passed through a miniature gas-meter calibrated in litres. In some cases more detailed studies of respiratory function were made at the Institute of Diseases of the Chest, Brompton Hospital, with the co-operation of Dr. F. J. Prime (Table II). In subjects who came to post-mortem examination the weights of the right and left ventricles were recorded separately by dividing the heart along the interventricular septum.

In previous papers (Simpson, 1954; Westlake, 1954*a*) we have discussed the

diagnosis and management of acute respiratory infections in bronchitic and emphysematous subjects; the following cases are presented to illustrate the main features of carbon dioxide narcosis occurring as a complication of oxygen therapy. The full details of arterial blood gases and pH before, during, and after oxygen therapy are given in Table I and Figs. 1 to 4. The normal range of arterial blood pH is 7·35 to 7·45, of arterial carbon dioxide tension 35 to 45 mm. Hg, and of plasma carbon dioxide content 54 to 66 volumes per cent.

Case Reports

Case 1. Papilloedema and raised intracranial pressure as a manifestation of respiratory failure. Rapid onset and recovery from carbon dioxide narcosis.

A housewife, aged 51 years, was admitted to hospital in November 1950 with acute bronchiolitis. She had complained of chronic cough since pertussis in childhood, and of progressively increasing dyspnoea on exertion since 1946. On examination she was restless, confused, and deeply cyanotic (oxygen saturation 45 per cent.), with rapid, gasping respirations at a rate of 54 to 60 per minute. Mild congestive cardiac failure was present. Neurological findings were normal except for early bilateral papilloedema, and the retinal veins were deep black in colour, extremely engorged, and tortuous. The plasma CO_2 content was increased to 91 volumes per cent., and the cerebrospinal fluid pressure was 500 to 600 mm. Within 20 minutes of starting oxygen therapy the patient lapsed into coma, the pupils were widely dilated, and there was coarse myoclonic jerking of the trunk and arms. The tendon-reflexes disappeared; the plantar responses remained flexor. The arterial oxygen saturation was now 100 per cent., and the plasma CO_2 content had risen by 18 volumes to 109 volumes per cent. Five minutes after discontinuing oxygen therapy consciousness was regained and the patient sat up and talked rationally, although she was again deeply cyanotic and dyspnoeic. This sequence of events could be repeated at will. She remained in the oxygen tent, and during the next four days continued to be stuporose and drowsy; when awakened by vigorous shaking she was irrational and complained of headache. Intermittent fine twitching of the small muscles of the lips and face, with jerking of the fingers, was a prominent feature. Oxygen was discontinued on the sixth day because cardiac failure had now disappeared, the fundi were normal, and her mental state was lucid. Three further episodes of respiratory infection requiring oxygen therapy were observed (December 1950, February 1951, and April 1951), and on each occasion stupor, coma, and irrationality with muscular twitching lasting three or four days were observed. There was, however, no evidence of any permanent mental impairment. In November 1951 persistent congestive cardiac failure with tricuspid incompetence supervened, and proved intractable to all forms of therapy. Death occurred suddenly in May 1952. Necropsy confirmed the diagnosis of structural emphysema and cor pulmonale (heart weight 516 gm.; right ventricle 218 gm., left ventricle 151 gm.). The brain was normal.

Comment. Carbon dioxide narcosis usually has a gradual onset during the first few days of oxygen therapy, but similar cases in which coma has supervened within a few minutes of the administration of oxygen, with equally rapid recovery of consciousness on exposure to room air, have been described by Godfrey, Pond, and Wood (1948), Donald (1949), and Motley (1950). Respiratory failure causes arterial oxygen unsaturation and retention of carbon dioxide.

The early papilloedema and raised intracranial pressure observed in this case are ascribed to the combination of anoxia, acidaemia, and hypercapnia causing dilatation of the cerebral and retinal vessels (Wolff and Lennox, 1930; Simpson, 1948; Westlake and Kaye, 1954). Despite relief of anoxic cerebral vasodilatation, intracranial pressure may remain elevated during oxygen therapy (compare Case 4) owing to the further increase in arterial pCO_2 and hydrogen ion concentration.

Case 3. The dangers of the administration of morphine to patients in respiratory failure.

An electrical fitter, aged 53 years, fell ill on January 3, 1951, with acute bronchiolitis. On January 5, 1951, he became dyspnoeic and confused, and would

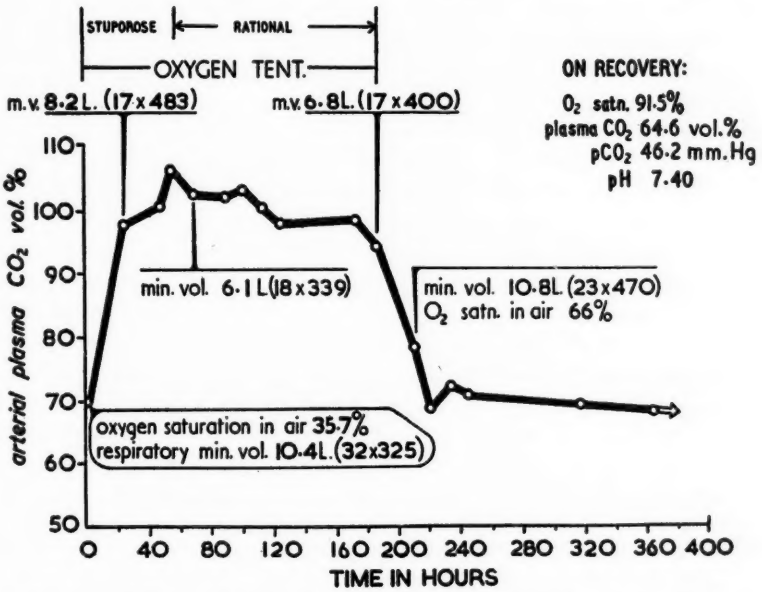

FIG. 1. The influence of oxygen therapy on the mental state, pulmonary ventilation, and arterial plasma carbon dioxide content in Case 3.
m.v. (min. vol.) = respiratory minute-volume in litres (respiratory rate and volume (ml.) in parentheses).

not remain in bed. His doctor, summoned at 1 a.m., found his blood-pressure raised to 230/130, and administered morphia gr. $\frac{1}{4}$. After this the patient became noticeably cyanotic, and lapsed into semicoma, lying staring at the ceiling. His breathing was so shallow that his daughter frequently put her ear to his chest to discover whether he were still alive. By 9 a.m. he had recovered consciousness and was rational, but cyanotic and dyspnoeic. On admission four hours later he appeared desperately ill. In spite of gross anoxaemia (oxygen saturation 35·7 per cent.) he was co-operative and able to give a moderately clear history. The respiratory minute-volume with the patient breathing air was 10·4 litres (Fig. 1). He was placed in an oxygen tent, and obtained immediate relief of dyspnoea and cyanosis. During the first 55 hours, though fully

oxygenated, he was drowsy, confused, and irrational. Periods of hypomanic activity, in which he recited the alphabet out loud, sang in a raucous voice, or attempted to struggle out of the tent, alternated with periods of stupor when he was barely rousable. During this period the arterial plasma CO_2 content rose to a peak of 106 volumes per cent. (37 volumes above the level found on admission). On the fourth day he was rational, although cerebration was slow. The respiratory minute-volume had fallen to 6·1 litres (Fig. 1). Thereafter his mental state remained lucid. Oxygen therapy was finally discontinued after 186 hours. On the following morning he was again cyanotic (oxygen saturation 66 per cent.) and mildly dyspnoeic. The increase in ventilation to 10·8 litres per minute had washed out a considerable quantity of carbon dioxide, and the level in the plasma had fallen by 16 volumes to 78 volumes per cent. On full recovery respiratory function tests (Table II) confirmed the diagnosis of mild emphysema. Radiographs of the spine showed advanced ankylosing spondylitis. The maximum breathing capacity was reduced to 38 litres per minute. The resting pulmonary ventilation was nine to ten litres per minute, and the respiratory response to inhalation of carbon dioxide was just below the lower limit of normal (Table II).

Comment. Before admission this patient had been subjected to a near-lethal degree of anoxia by the injudicious administration of morphine. In animal experiments exposure to low oxygen tensions depresses the sensitivity of the respiratory centre to carbon dioxide (Newburgh, Means, and Porter, 1916; Moyer and Beecher, 1942; Ivy, Grodins, Adler, and Snapp, 1947). Thus it is probable that the major portion of the respiratory minute-volume (10·8 litres per minute) on admission was maintained by the stimulus of anoxia rather than carbon dioxide tension. During oxygen therapy the relief of anoxia allowed ventilation to fall below the patient's normal resting level (to between six and seven litres per minute), and consequently the arterial carbon dioxide content rose until a higher level of arterial pCO_2 and hydrogen ion concentration balanced the missing anoxic stimulus and a new respiratory equilibrium was achieved.

Case 4. Transient carbon dioxide narcosis, with spontaneous recovery on continuing oxygen therapy.

A lorry driver, aged 53 years, was admitted with acute bronchitis on January 10, 1951. He was rational, and could give an accurate history. Moderate cyanosis, orthopnoea, and profuse sweating on the forehead were noted. The blood-pressure was 175/85. The arterial oxygen saturation was 65·5 per cent. At 4 p.m. he was placed in an oxygen tent, and there was immediate relief of dyspnoea and cyanosis, and cessation of sweating. He said he felt much better, and asked for some tea. Three hours later he became restless, and complained that he felt queer and had lost the use of his legs. He looked dazed and uncomfortable, and fumbled purposelessly with the sheets. Though fully oxygenated, he was confused and disorientated. Intermittent fine twitching of the fingers had appeared. An arterial sample taken at 8 p.m. showed a rise in plasma CO_2 content of 11 volumes per cent. (73 to 84 volumes) (Fig. 2). During the next 30 minutes he sank slowly into semicoma, lying with the eyes widely opened and staring straight ahead. All the limbs were held rigidly in flexion. Constant fine twitching movements of the fingers and coarser tremors of the arms were prominent. Pinching the tendo Achillis elicited a mild withdrawal reaction, but

there was no response to closing his eyes, moving the limbs, or applying a blood-pressure cuff. Both plantar responses were flexor, and the tendon-reflexes were present and equal but diminished. The blood-pressure had risen to 205/95. He remained semicomatose for a further five hours. He could then be wakened, but complained of severe headache and was mentally confused. Next day he was lucid, and remained so for the remaining six days in the tent. The arterial

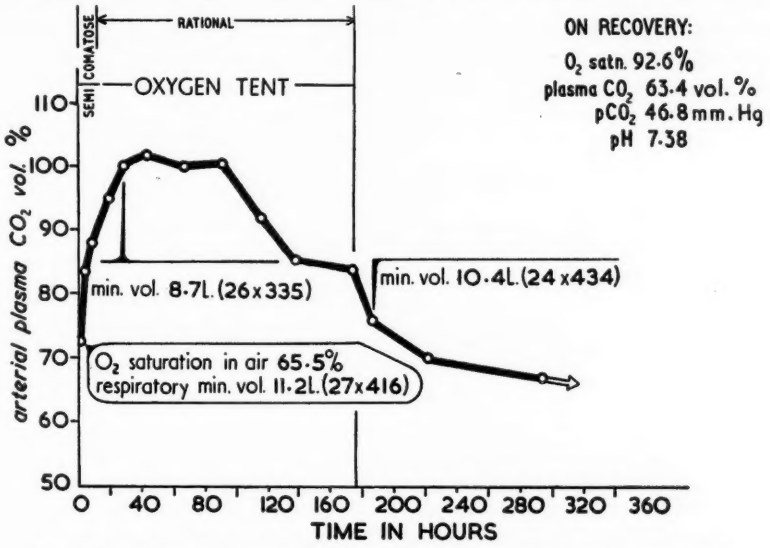

FIG. 2. The influence of oxygen therapy on the mental state, pulmonary ventilation, and arterial plasma carbon dioxide content in Case 4.
(Respiratory rate and volume (ml.) in parentheses.)

plasma CO_2 content continued to increase, and reached a peak of 102 volumes per cent. after 50 hours. Lumbar puncture performed after 75 hours' continuous oxygen therapy showed that the cerebrospinal fluid pressure was 285 to 305 mm.

Comment. Initially the effect of oxygen therapy was entirely beneficial, but within a few hours symptoms reminiscent of the first stages of anaesthesia—restlessness, anxiety, and mental confusion—had appeared, and were rapidly followed by a period of narcosis lasting five hours. On the following day the patient was mentally lucid, although the carbon dioxide content of the arterial plasma had still further increased. This fact indicates that mental disturbance cannot be related to total carbon dioxide content, but subsequent more detailed studies have established a relationship to arterial pH and pCO_2 (page 166, Table III). The bicarbonate ion itself is not known to have any neurological effects.

Case 5. Cerebral adaptation to hypercapnia. Failure of respirator to increase pulmonary ventilation.

A retired man, aged 62 years, was admitted to hospital in February 1954 with an acute pneumococcal bronchitis. He was rational and mentally orientated, although he had complained of visual and auditory hallucinations during the previous two weeks. He had moderate respiratory failure, with the arterial CO_2

tension rasied to 72 mm. Hg, pH 7·26, plasma CO_2 content 74 volumes per cent., and oxygen saturation 64 per cent. A chest radiograph showed clear lung fields. He was treated with penicillin, streptomycin, and continuous oxygen in a tent. After four hours' oxygen therapy he became semicomatose, with coarse myoclonic jerking of the arms and profuse sweating: the plasma CO_2 content was found to have risen to 83 volumes per cent., with an increase in arterial pCO_2 to 105 mm. Hg and a fall in pH to 7·13 (Fig. 3). By the following day he had regained consciousness and was rational, though rather drowsy. Renal excretion

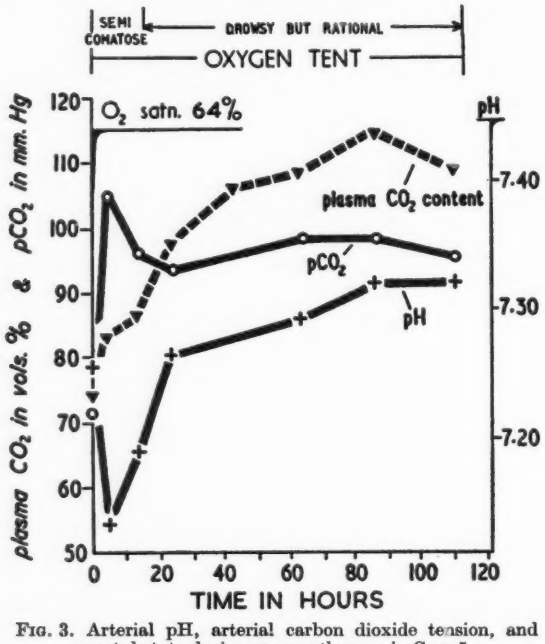

FIG. 3. Arterial pH, arterial carbon dioxide tension, and mental state during oxygen therapy in Case 5.

of electrolytes had restored the pH to the level found on admission (pH 7·26), and the pCO_2 had fallen to 93 mm. Hg. During subsequent days the arterial pH continued to rise slowly toward normal, and the pCO_2 was maintained at a plateau level of 92 to 96 mm. Bronchospasm disappeared, and the sputum became mucopurulent, yielding a growth of *Bact. coli* only. This improvement was not maintained, and on the seventh day he became semicomatose, with a rise in arterial pCO_2 to 121 mm. Hg and a fall in pH to 7·12. Donald's (1954) patient-cycled positive pressure respirator was used in an attempt to increase ventilation, but after 30 minutes the arterial pH and pCO_2 were unchanged, and the use of the machine was abandoned. The patient died 10 hours later. Post-mortem examination showed gross structural emphysema of the lungs with formation of bullae, mild acute bronchitis with a little mucoid secretion in the trachea and main bronchi, and no bronchopneumonia. The weight of the heart was within normal limits (310 gm.), but the right ventricle was hypertrophied (right ventricle 123 gm., left ventricle 113 gm.)

Comment. Semicoma, with myoclonic jerking and profuse sweating, was caused by the combination of high arterial carbon dioxide tension (105 mm. Hg)

and severe acidaemia (pH 7·13). When the kidney had restored the arterial pH to the initial level (7·26) hypercapnia alone was insufficient to cause mental disturbance, and mental lucidity was maintained with a carbon dioxide tension of 92 to 96 mm. Hg—20 mm. or more above the initial level. Eventual deterioration despite control of the bronchial infection was unexpected.

Case 7. Progressive respiratory failure unaffected by intravenous infusion of alkali.

A factory worker, aged 67 years, was admitted to hospital on January 20, 1953, with bilateral basal bronchopneumonia and congestive cardiac failure. He was

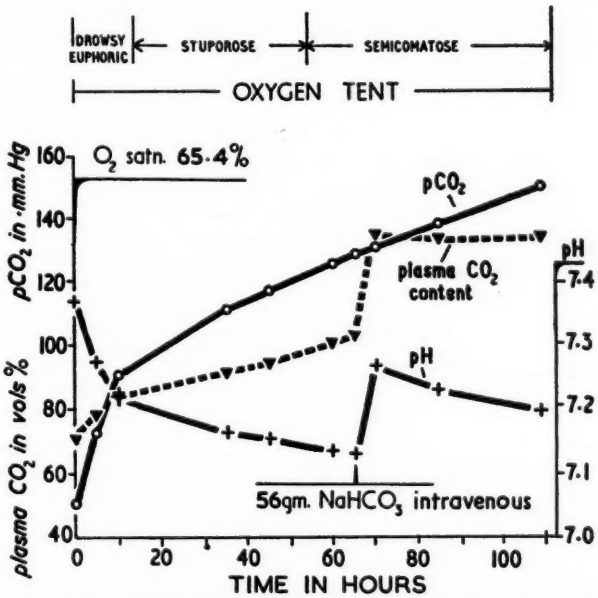

FIG. 4. Case 7. Progressive respiratory failure during oxygen therapy. Note the failure of alkali administration to alter the rate of rise of arterial carbon dioxide tension.

known to have advanced emphysema, with restriction of the maximum breathing capacity to 22 litres per minute. He was moderately cyanotic (oxygen saturation 65·4 per cent.), with mild carbon dioxide retention (pCO_2 52 mm. Hg) but a normal blood pH (7·38). After 12 hours in the tent he was conscious, but disorientated and euphoric. He sang at the top of his voice, and kept the ward amused by cheerful banter. He sank slowly into stupor, and after 35 hours the pH had fallen to 7·16 and the pCO_2 had risen to 110 mm. Hg (Fig. 4). After 65 hours he was semicomatose and unable to take fluids by mouth (pH 7·13; pCO_2 129 mm). Fifty-six gm. of sodium bicarbonate were administered intravenously. This raised the arterial pH to 7·26, but there was no change in the level of consciousness. He remained in coma, and died on January 28, 1953, with acute pulmonary oedema, the pH falling to 6·81. Post-mortem examination showed gross structural emphysema with formation of bullae and patchy bronchopneumonia. The heart weighed 390 gm. (right ventricle 155 gm., left ventricle 170 gm.).

Comment. Carbon dioxide narcosis is usually a transient condition which spontaneously improves, but in a minority of cases progressive respiratory failure, with rising arterial carbon dioxide tension and falling pH, proves fatal. Alkali was administered on the supposition that the acidaemia might be a factor in perpetuating respiratory failure by depressing the medullary respiratory centre. But raising the arterial pH to 7·26 made no difference to the level of consciousness, respiratory activity was unchanged, and the carbon dioxide tension continued to rise at its previous rate.

Case 8. The successful emergency treatment of carbon dioxide narcosis.

A man, aged 52 years, was admitted to hospital on January 5, 1954, with a confluent left basal bronchopneumonia, early congestive cardiac failure, and moderate respiratory failure (oxygen saturation 53·4 per cent., pH 7·33, and pCO_2 66 mm. Hg). He was rational and able to give a good history. No gallop rhythm was audible on auscultation of the heart, and the blood-pressure was 120/70. He was treated with penicillin and oxygen by B.L.B. mask (six to seven litres per minute). Three hours later he was comatose, respirations were so shallow as to be almost imperceptible, a loud diastolic gallop rhythm was audible over the xiphisternum, and the blood-pressure had fallen to 90/20. Arterial blood analysis showed that the pH had fallen to 7·07, with a rise in pCO_2 to 102 mm. Hg. Manual artificial respiration was applied, together with the rapid intravenous injection of 15 ml. of nikethamide, followed by aminophylline (0·5 gm.) and digoxin (0·5 mg.). Oxygen was temporarily discontinued, and then resumed at a flow of two to three litres per minute by light-weight 'polymask'. Three hours later he was again conscious and able to answer questions; the gallop rhythm had disappeared, and the blood-pressure had risen to 120/55. Subsequent culture of the sputum revealed a profuse growth of *Haemophilus influenzae*, and the antibiotic was changed from penicillin to chloramphenicol. Thereafter recovery was slow but uneventful. The patient remains a respiratory cripple, the maximum breathing capacity fluctuating between 21 and 43 litres per minute.

Comment. The development of gallop rhythm during an episode of acute carbon dioxide narcosis is of considerable interest. Lange, Craig, Tchertkoff, Oberman, and LoCasto (1951) have shown that severe acidaemia has a direct action on the heart, causing a considerable increase in cardiac output. This stimulus acting on the failing myocardium might well cause a gallop rhythm to appear or precipitate an exacerbation of congestive cardiac failure.

Case 9. Carbon dioxide narcosis in status asthmaticus.

A pathologist, aged 58 years, was admitted to hospital in status asthmaticus on September 13, 1951. On examination she appeared exhausted and mildly dehydrated, but her mental state was normal. She insisted on giving herself continuous oxygen therapy by B.L.B. mask. At 7 a.m. on September 14, 1951, she became drowsy, and rapidly lapsed into unrousable coma. The extremities were warm and sweating. A few distant rhonchi were audible on auscultation of the chest. The blood-pressure was 120/80. The limbs were flaccid, with absent tendon-reflexes and flexor plantar responses. There was no twitching. Arterial blood analysis showed an extreme respiratory acidaemia (oxygen saturation 92 per cent., pH 6·88, and pCO_2 193 mm. Hg). In spite of repeated

bronchoscopy and massive doses of adrenaline (4 ml. subcutaneously every hour) she remained in coma and died 28 hours later. Post-mortem examination showed generalized microscopic emphysema, without formation of bullae. The majority of the smaller bronchi and bronchioles were occluded by a tenacious white exudate. The heart was normal. The cerebral vessels were congested, but the brain was otherwise normal.

Comment. Carbon dioxide narcosis complicating status asthmaticus has been reported by Beale, Schiller, Halperin, Franklin, and Lowell (1951) and Hickam, Sieker, Pryor, and Ryan (1952). When extreme bronchospasm and obstruction with mucus reduce pulmonary ventilation below the normal resting level, carbon dioxide retention inevitably occurs and may lead to irreversible respiratory failure.

Case 13. Carbon dioxide narcosis misdiagnosed as left ventricular failure.

A lorry driver, aged 46 years, was admitted to hospital on January 3, 1952, in congestive cardiac failure with a left-lower-lobe bronchopneumonia. The blood-pressure was 150/80. Penicillin therapy was started, but he was not considered to need oxygen. Three days later his condition deteriorated, with restlessness and increased cyanosis. A mixture of 10 per cent. carbon dioxide in oxygen was administered by a nurse. Shortly afterwards he lapsed into coma. When seen by the house physician he was deeply comatose and sweating profusely; the skin was cold, the blood-pressure 200/120, and râles were audible at both bases; the knee- and ankle-jerks were absent, but the plantar responses were flexor. Cardiac infarction with left ventricular failure was diagnosed, and the patient was transferred to an oxygen tent. Morphine gr. $\frac{1}{3}$ was administered. During the day he remained unconscious, sweating profusely, but there were no localizing neurological signs. The cerebrospinal fluid pressure was over 300 mm., but the fluid was normal in other respects. On the following day he was drowsy and mildly confused, but could be roused to answer simple questions. The degree of congestive failure had increased, and bilateral papilloedema was present. Arterial blood analysis revealed moderate acidaemia and hypercapnia (pH 7·29, pCO_2 92 mm. Hg). With digitalis and mersalyl cardiac compensation was restored, and the patient was discharged free from oedema on January 28, 1952.

Comment. Carbon dioxide narcosis was precipitated in this case by the administration of a mixture of carbon dioxide in oxygen, and maintained for a further 18 hours by morphine. Familiarity with the syndrome would have prevented this error.

Discussion

The narcotic action of carbon dioxide in high concentration has been known since the pioneer observations in anaesthesia of Hickman in 1820 (Thompson, 1912). Waters (1937) successfully anaesthetized three patients with 30 per cent. carbon dioxide, but he considered that the method had no practical application, since one subject had a convulsion on the operating table. Human susceptibility to inhaling carbon dioxide varies, but 7·6 per cent. appears to be the lowest concentration that will induce narcosis (Dripps and Comroe, 1947). Most people lose consciousness after taking eight to 12 breaths of 30 per cent. carbon dioxide, a procedure which causes a rise in arterial carbon dioxide tension (pCO_2) to more

than 100 mm. Hg and consequent lowering of the arterial pH to below 7·1 (Meduna, 1950). The ultimate basis of the narcotic action of carbon dioxide probably resides in an interference with intracellular enzyme systems, since it is well known that their activity is greatly altered by small changes in pH. In diabetic coma, for example, cerebral oxygen consumption is diminished in spite of a normal arterial oxygen saturation and increased cerebral blood-flow; and Kety, Polis, Nadler, and Schmidt (1948) have postulated that acidaemia may

TABLE III

Relationship between Arterial pH, Arterial Carbon Dioxide Tension, and Mental State during Oxygen Therapy

Mental state	*Arterial pH*					*Arterial pCO_2 (mm. Hg)*				
	7·4–7·3	*7·3–7·2*	*7·2–7·1*	*7·1–7·0*	*<7·0*	*40–60*	*60–80*	*80–100*	*100–120*	*>120*
Conscious	14	14	0	0	0	3	12	11	2	0
Drowsy or stuporose	3	8	7	0	0	0	3	10	5	0
Semicomatose	0	4	10	2	0	0	0	3	5	8
Comatose	0	0	0	3	4	0	0	0	1	6

contribute to the depression of cerebral function by interfering with the mechanism responsible for cellular uptake of oxygen. In diabetic acidosis the arterial pCO_2 is low, while in carbon dioxide narcosis it is raised. Jacobs (1920) has shown that when the blue flowers of the Russian comfrey are floated in a slightly alkaline solution of sodium bicarbonate (pH 7·4) diffusion of carbon dioxide through the cell-membrane gives rise to an intracellular acidosis and the petals turn red. Thus hypercapnia may augment the effect of arterial acidaemia in lowering intracellular pH, and so depressing cerebral oxygen consumption upon which the maintenance of consciousness depends.

The relationship between acidaemia, hypercapnia, and mental state is shown in Table III, compiled from 69 observations on 21 emphysematous patients who were receiving oxygen therapy. It is seen that, with few exceptions, mental clarity was present with an arterial pH above 7·3 or pCO_2 below 80 mm. Hg, and semicoma or coma with a pH below 7·1 or pCO_2 above 120 mm. Hg, and that between these values the mental state deteriorated as the pH fell and the pCO_2 increased. Mental disturbance was present in all patients when the pH fell below 7·2 or the pCO_2 rose above 120 mm. Hg. It is not usually possible to assess the relative contributions of acidaemia and hypercapnia to depression of cerebral function, and it must be assumed that mental disturbance is due to their combined effect on the metabolism of cerebral neurones. In some instances, however, the predominant factor is acidaemia or hypercapnia alone. We have recently studied a patient with bilateral ureterocolic transplantation and acute pyelonephritis, in whom the arterial pH fell to 7·07 and pCO_2 to 13 mm. Hg (Westlake, 1954*b*). Consciousness was restored by the infusion of alkali, even though the level of blood-urea continued to rise; coma was therefore ascribed to acidaemia rather than uraemia. Extreme hypercapnia alone may cause coma. For example, one patient (Case 7) was conscious but mildly disorientated with

an arterial pH of 7·22 and pCO_2 of 89 mm. Hg. After further oxygen therapy for 70 hours, when the pH was at the same level, he had become semicomatose, but the pCO_2 had now risen to 140 mm. Hg (see Fig. 4). The summation of the cerebral effects of hydrogen ion concentration and carbon dioxide tension explains why the symptoms of carbon dioxide narcosis usually appear during the first 24 hours of oxygen therapy, when the carbon dioxide content of the blood is rising rapidly, causing both hypercapnia and an uncompensated acidaemia,

TABLE IV

Hypercapnia without Mental Symptoms in a Patient aged 64 Years during Oxygen Therapy

	Arterial blood					
Date	*Oxygen saturation* (%)	*pH*	*Plasma Co_2* (*vols.* %)	*pCO_2* (*mm. Hg*)	*Mental state*	*Oxygen administered*
5.4.54	89	7·26	91·4	88	Normal	By nasal catheter, starting with 2 litres a minute and gradually increasing
23.4.54	83	7·35	110	87	,,	,,
28.4.54	91	7·26	114	110	,,	,,
3.5.54	85·5	7·33	105	87	,,	,,
8.5.54	99	7·31	103·4	90	,,	,,
21.6.54	82	7·36	111	86	,,	In oxygen tent
22.6.54	87·5	7·38	118	88	,,	,,

mental lucidity being regained within the next few days as the pH is restored to more normal levels by the kidneys (compare Cases 3, 4, and 5). If the arterial carbon dioxide increases slowly, so that the pH is relatively undisturbed, considerable cerebral adaptation to hypercapnia can be achieved. This fact is clearly shown in Table IV. But there is a limit to the rise in arterial pCO_2 (with pH near normal) which may occur without mental symptoms appearing. From Table III the critical level appears to be between 110 and 120 mm. Hg.

The general effects of inhaling carbon dioxide. The inhalation of low concentrations of carbon dioxide (7 to 12 per cent.) has a powerful stimulant action on the medullary vasomotor, sudorimotor, and respiratory centres, causing tachycardia, peripheral vasoconstriction, moderate rise in blood-pressure, sweating, and hyperpnoea (Seevers, 1944; Dripps and Comroe, 1947). There is, however, no change in cardiac output (Kety and Schmidt, 1948). The rectal temperature falls (Brown, 1930). With higher concentrations (20 to 30 per cent.) a central depressant effect becomes more evident, and ventilation decreases (Friedländer and Herter, 1879; Leake and Waters, 1929). Lange, Craig, Tchertkoff, Oberman, and LoCasto (1951) have shown in animal experiments that severe acidaemia (pH 7·1 or less) causes a large increase in cardiac output (up to three- or fourfold), but peripheral vascular resistance is disproportionately decreased, so that the blood-pressure falls to basal or even hypotensive levels. The general effects of inhaling increased concentrations of carbon dioxide closely correspond to the clinical picture seen in carbon dioxide narcosis: warm, sweating extremities, bounding pulse, low blood-pressure, hypothermia, and mental clouding or

coma. In one subject (Case 8) carbon dioxide narcosis was associated with the development of gallop rhythm, and in another (Case 13) with increase in the degree of congestive cardiac failure.

The neurological effects of carbon dioxide. 1. *Motor phenomena.* Muscular movements are a characteristic feature of carbon dioxide narcosis (Leake and Waters, 1929). They usually consist of fine tremors of the facial muscles with intermittent jerking of the fingers and arms (compare Cases 1, 4, and 5), but gross clonic movements of the limbs may occur (Davies and Mackinnon, 1949), or even convulsions (Hickam, Sieker, Pryor, and Ryan, 1952). In one of our subjects clonic limb movements were so violent that two nurses were required to prevent the patient from falling to the floor. Physiologists studying the effect of carbon dioxide on animals (Leake and Waters, 1929) and psychiatrists observing therapeutic inhalation in man (Leake, Wood, Botsford, and Guedel, 1930; Kelman, 1932; d'Elseaux and Solomon, 1933; Meduna, 1950) have all noted similar motor phenomena. In discussing a fatal case of carbon dioxide poisoning during nitrous-oxide-ether anaesthesia, Waters (1937) wrote: 'Twitching of the smaller facial muscles is the commonest sign of carbon dioxide excess in anaesthesia; if they are disregarded a more or less generalised mild convulsive manifestation may follow.' It is a matter of clinical observation that similar movements may occur in a markedly anoxic emphysematous patient in whom the arterial pCO_2 is not high, and with oxygen therapy they may at first disappear, only to reappear as the arterial pCO_2 and hydrogen ion concentration rise. Pollock (1949) has shown that carbon dioxide depresses cortical excitability and antagonizes convulsions induced by metrazol or electrical stimulation. Thus muscular movements observed during carbon dioxide narcosis probably arise from neural levels lower than the cortex. King, Garrey, and Bryan (1932) investigated the effect of carbon dioxide on the knee-jerk of the dog, and found that this reflex was depressed or abolished by the action of inhibitory impulses descending from the cerebrum to the spinal cord. In clinical cases of carbon dioxide narcosis the plantar responses either disappear or remain flexor (compare Cases 1, 3, 7, 8, and 13); but in very deep therapeutic narcosis Meduna (1950) has occasionally been able to elicit an extensor plantar response.

2. *Effects on cerebrospinal fluid pressure.* Carbon dioxide causes cerebral vasodilatation, with a rise of intracranial pressure (Dixon and Halliburton, 1914; Wolff and Lennox, 1930; Goldensohn, Whitehead, Parry, Spencer, Grover, and Draper, 1951) and increased cerebral blood-flow (Kety and Schmidt, 1948; Patterson, Heyman, and Duke, 1952). Clinically these effects are associated with headache and the development of papilloedema (compare Cases 1, 3, and 13). There is no evidence that raised intracranial pressure *per se* (when unaccompanied by reduced cerebral blood-flow) has any deleterious effect on the function of cerebral neurones. Mental disturbance during oxygen therapy appears to have no direct causal relationship to a concomitant rise in intracranial pressure, for reasons fully discussed in a previous paper (Westlake and Kaye, 1954). Lumbar puncture has no place in the management of carbon dioxide narcosis.

Respiratory failure and the genesis of carbon dioxide narcosis. Respiratory failure may be said to be present when there is failure or inability of the respiratory centre and neuromuscular mechanism to prevent the arterial pCO_2 from rising above the normal upper limit of 45 to 48 mm. Hg (Westlake, 1954*a*). Many emphysematous subjects have chronic respiratory failure, with the resting arterial pCO_2 reaching a level of 70 to 80 mm. Hg (Baldwin, Cournand, and Richards, 1949), but in those in whom the level is normal when they are well an acute respiratory infection will often precipitate respiratory failure (compare Cases 3, 4, 6, 8, and 10, Table I). Scott (1920) observed that the respiratory response to carbon dioxide in emphysema was diminished, and this observation has been confirmed by Meakins and Davies (1925), Taquini, Fasciolo, Suarez, and Chiodi (1948), and Donald and Christie (1949). Prime and Westlake (1954) have shown that the response is correlated with the degree of carbon dioxide retention, diminishing with increasing levels of arterial pCO_2, so that at a level of 65 to 75 mm. Hg it is only 10 to 20 per cent. of normal. Thus in respiratory failure an increasing proportion of the total ventilation is maintained by an anoxic drive from the carotid and aortic chemoreceptors, and relief of anoxia may then be followed by a severe fall in ventilation. An inevitable consequence of a fall in ventilation is that the alveolar pCO_2 rises and is accompanied by a corresponding arterial rise in pCO_2 and fall in pH. In Case 3, for example, the pulmonary ventilation fell by 40 per cent. during oxygen therapy (from 10·8 to 6·1 litres; see Fig. 1). If the decrease in ventilation is sufficiently large, carbon dioxide narcosis will ensue. Motley (1950) has suggested that the respiratory centre becomes entirely insensitive to carbon dioxide, but the facts are more easily explained by assuming that ventilation falls until a higher pCO_2 and hydrogen ion concentration balance the inhibitory effect of relief of anoxia. Thus administration of 10 per cent. carbon dioxide in oxygen to a patient in coma from spontaneous carbon dioxide narcosis (Davies and Mackinnon, 1949) was still capable of increasing ventilation.

The exact mechanisms by which chest infection causes respiratory failure in emphysematous subjects are still under investigation, but the following factors appear important: (1) Impairment of respiratory sensitivity to carbon dioxide by previous exposure to anoxia (Moyer and Beecher, 1942; Ivy, Grodins, Adler, and Snapp, 1947). A clinical example has already been described (Case 3). (2) Diminution of maximum breathing capacity by respiratory obstruction and increased visco-elastic resistance of the lungs. (3) A high metabolic rate consequent on the marked increase in the work of breathing (Riley, 1954). It is evident that the prevention of carbon dioxide narcosis lies in the prompt and effective treatment of the causal respiratory disturbance.

The treatment of carbon dioxide narcosis. If oxygen therapy relieves dyspnoea some increase of the arterial carbon dioxide content must occur, but this increase is often insufficient to cause symptoms (Fig. 5). In other cases transient carbon dioxide narcosis occurs, with spontaneous recovery even if oxygen therapy is continued, and no treatment is required (compare Cases 3, 4, and 5). In a minority of patients, however, severe acidaemia and hypercapnia cause coma,

sputum is retained, and there is a grave risk of aspiration pneumonia, pulmonary atelectasis, and progressive respiratory failure. Carbon dioxide narcosis was probably a major factor in the fatal outcome in Cases 5, 7, 9, 11, 14, and 16, and similar instances have been reported by other authors (Davies and Mackinnon, 1949; Wilson, Borden, Ebert, and Wells, 1950; Callaway and McKusick, 1951). The emergency treatment of severe carbon dioxide narcosis is admittedly unsatisfactory, since it usually occurs in subjects with advanced respiratory im-

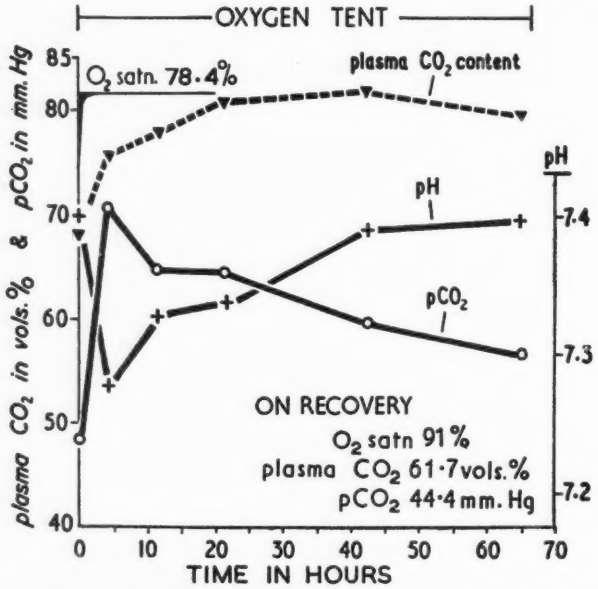

FIG. 5. Influence of oxygen therapy on the arterial pH, arterial carbon dioxide tension, plasma carbon dioxide tension, and plasma carbon dioxide content in a woman of 59 years who had acute bronchitis. There was no mental disturbance at any period.

pairment. The following manœuvres, however, may succeed (compare Case 8). Rapid intravenous injection of 10 to 15 ml. of nikethamide will give the failing respiratory centre a temporary stimulus, and can be repeated at intervals of two to three hours. If oxygen therapy has been started by tent, it should be discontinued and replaced by oxygen at low rates of flow (one to three litres per minute) by nasal catheter or light-weight face mask (Barach, 1948; Simpson, 1954). The rate of flow should be adjusted so that the arterial oxygen saturation is raised no higher than 80 to 85 per cent.; this level is sufficient to prevent death from acute anoxia, but not so high that the reflex anoxic respiratory drive from the carotid body is completely inhibited. Further efforts should be made to treat the causal respiratory disturbance more effectively, for example by change of antibiotic, bronchoscopic aspiration of retained secretions, and administration of corticotrophin or cortisone to relieve intractable bronchospasm. Boutourline-Young and Whittenberger (1951), Stone, Schwartz, Newman, Felt-

man, and Lovelock (1953), and Lovejoy, Yu, Nye, Joos, and Simpson (1954) have claimed that carbon dioxide narcosis can be successfully treated by mechanical artificial respiration. In our experience it has been impossible to synchronize the patient's spontaneous respiratory efforts with those of the machine. In theory a patient-cycled respiratory apparatus should be more effective, but in the one subject (Case 5) with whom it has been tried ventilation was not increased. This problem needs further study since, if effective means of maintaining ventilation were devised, oxygen therapy would have no adverse effects.

With growing awareness of the potential hazards oxygen therapy is used infrequently in some centres (Flint, 1954). This is a mistaken policy, since exposure to prolonged anoxia has many deleterious effects. (1) Severe anoxia causes sudden cardio-respiratory failure (Kritzler, 1944), and if recovery from coma does occur there may be permanent mental impairment and residual neurological sequelae (Courville, 1936). (2) Anoxia reduces the respiratory response to carbon dioxide, and may thus initiate respiratory failure and carbon dioxide narcosis. (3) Anoxia initiates a vicious circle of pulmonary oedema, with further increase in the degree of anoxia (Drinker, 1945). (4) Anoxia is one of the factors responsible for precipitating congestive cardiac failure in subjects with pre-existing cor pulmonale (Motley, Cournand, Werkö, Himmelstein, and Dresdale, 1947). It is our belief that the benefits of oxygen therapy carefully used outweigh its dangers, and we have now adopted Barach's (1948) method, which consists of gradually increasing the oxygen supply to the patient. Oxygen is given by nasal catheter or light-weight face mask at a rate of one to three litres per minute, and the flow is increased only if mental symptoms are not seen. In this way we have avoided such symptoms, which we feel sure would have been produced had a tent been used. An alternative method of avoiding carbon dioxide narcosis during oxygen therapy has been described by Donald (1953): the canopy of the oxygen tent is rolled up and the patient allowed to breathe room air for 20 minutes in every hour. The short period of exposure to anoxia increases ventilation sufficiently to prevent a progressive rise in arterial carbon dioxide tension.

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Summary

1. The clinical and biochemical findings in 16 cases of carbon dioxide narcosis have been reviewed. All the patients had pre-existing respiratory impairment, and were being treated by oxygen therapy during an acute respiratory disturbance.

2. Carbon dioxide narcosis is characterized by mental disturbance ranging from confusion, mania, or drowsiness to profound coma, and is associated with headache, sweating, muscle twitching, raised intracranial pressure, and occasionally papilloedema.

3. A close parallel can be drawn between symptoms seen after oxygen therapy and those arising in man and animals from inhalation of high concentrations of carbon dioxide.

4. There is a relationship between arterial pH, arterial carbon dioxide tension, and mental state: mental disturbance was usually present when the pH was less than 7·2 or the pCO_2 higher than 100 mm. Hg, and coma when the pH fell below 7·1 or the pCO_2 rose above 120 mm. Hg; most patients were conscious if the pH was above 7·3 or the pCO_2 less than 80 mm. Hg.

5. The cause of the neurological disturbance is the direct action of acidaemia and hypercapnia on the metabolism of cerebral neurones. In many cases carbon dioxide narcosis is a transient condition, with spontaneous recovery as the arterial pH is restored to normal by renal activity; in a minority it causes fatal respiratory failure.

6. The treatment of carbon dioxide narcosis is manifestly its avoidance, and for this purpose we advise the administration of oxygen in slowly increasing concentration by nasal catheter or face mask, starting with one to three litres per minute; alternatively oxygen can be administered in higher concentrations, with short periods of exposure to room air (20 minutes in every hour). Methods of treating carbon dioxide narcosis, if it occurs in spite of these precautions, are outlined, but as yet none is entirely satisfactory.

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THE TREATMENT OF PULMONARY TUBERCULOSIS WITH IPRONIAZID (1-ISONICOTINYL-2-ISOPROPYL HYDRAZINE) AND ISONIAZID (ISONICOTINYL HYDRAZINE)[1]

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(From the London Hospital)

In 1951 the thiosemicarbazone of isonicotinaldehyde was shown to be active against tuberculous infection in mice (Grunberg and Leiwant, 1951). In the synthesis of this thiosemicarbazone, isonicotinyl hydrazine was used as an intermediate (Fox, 1951). The latter substance (isoniazid) and its isopropyl derivative, iproniazid, were found to exert a striking and lasting effect upon the experimental tuberculosis of mice (Grunberg and Schnitzer, 1952), and subsequently proved to be effective against the disease in man (Robitzek, Selikoff, and Ornstein, 1952). The antituberculous and pharmacological properties of iproniazid and isoniazid were originally described in a series of papers appearing mainly in America during the early part of 1952; recorded differences between the two drugs are shown in Table I. The minimum concentration of iproniazid required to inhibit the H37Rv strain of *M. tuberculosis* for a 14-day period (0·16 to 0·31 mg. per 100 ml.) is approximately 60 times the equivalent concentration of isoniazid (0·0025 to 0·005 mg. per 100 ml.). There is, however, some variation according to the type of medium used. The figures quoted are those found in the Tween-albumin liquid medium and in the Proskauer and Beck synthetic medium (Steenken and Wolinsky, 1952). When iproniazid or isoniazid was given to mice infected with the H37Rv strain of *M. tuberculosis* no viable tubercle bacilli could be recovered after 21 days' treatment. The dose of iproniazid (25 mg. per kg. body-weight) required to achieve this result was two and a half times as great as the equivalent dose of isoniazid (10 mg. per kg. body-weight) (Grunberg and Schnitzer, 1952). In man the plasma levels of iproniazid were found to be more than twice as high as those of isoniazid, and to be better maintained (Lewis, 1952).

After the antituberculous properties of the hydrazine derivatives of isonicotinic acid had been reported during the early part of 1952, isoniazid was released for general use and was universally accepted as an effective antituberculous agent. The isopropyl derivative (iproniazid), on the other hand, was made available for clinical trials only in certain centres in America and in this country. When the first supply of iproniazid was received at the London Hospital, the only available information relating to its use in the treatment of pulmonary tuberculosis was contained in the original paper by Robitzek, Selikoff, and Ornstein (1952). Although this paper described the effects of both

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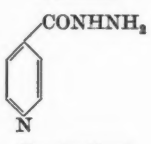
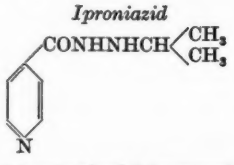
isoniazid and iproniazid against pulmonary tuberculosis, the great majority of patients were in fact treated with iproniazid, whereas in most subsequent trials, both in America and in Britain, isoniazid was used. No information relating to the comparative value of these two drugs was then available. Furthermore, the American workers had not reported the emergence of iproniazid-resistant strains during the treatment of pulmonary tuberculosis, nor had the effect of

TABLE I

Known Differences between Isoniazid and Iproniazid

	Isoniazid	*Iproniazid*
Chemical structure		
	Isonicotinyl hydrazine	1-isonicotinyl-2-isopropyl hydrazine
In vitro activity (Steenken and Wolinsky, 1952):		
Minimal bacteriostatic level	0·0025 mg./100 ml.	0·16 mg./100 ml.
In vivo activity (mice) (Grunberg and Schnitzer, 1952):		
No viable bacilli after 21 days' treatment with	10 mg. per kg. body-weight	25 mg. per kg. body-weight
Peak plasma levels		
Approximate amalgamation of results reported by:		
Elmendorf, Cawthon, Muschenheim, and McDermott (1952)		
Rubin, Drekter, Scheiner, and DeRitter (1952)	$\frac{1}{16}$ of dose per kg. body-weight	$\frac{1}{4}$ of dose per kg. body-weight
Lewis (1952)		
Present paper		

iproniazid against isoniazid-resistant infections been described. It was therefore decided to carry out at the London Hospital a series of clinical trials designed to compare the effects of isoniazid and iproniazid in patients with pulmonary tuberculosis, with special reference to bacterial resistance.

Preliminary Studies at the London Hospital

Two groups of patients with chronic cavitating fibrocaseous tuberculosis of the lungs were treated with 300 mg. iproniazid daily for periods of two to three months in 1952. The first group of eight patients had previously received treatment with isoniazid, and were yielding bacilli resistant to 1 μg. isoniazid per ml., or more, when iproniazid treatment was started. Except for increase in appetite and weight, none of the patients in this group showed any significant clinical or radiological response to iproniazid. Three of them deteriorated during treatment, and in at least one patient deterioration could be attributed to the exhibition of iproniazid (Ogilvie, 1954). Seven of the eight patients, including

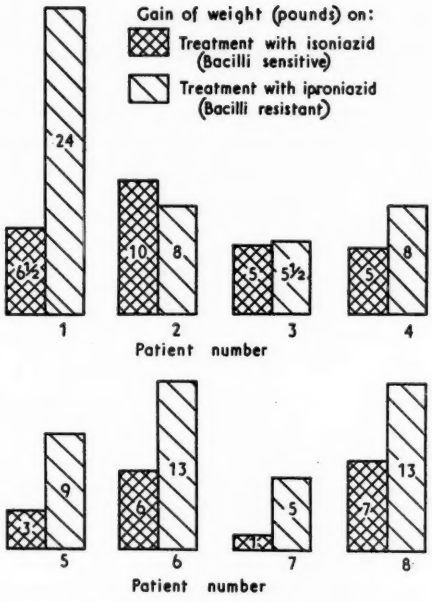


FIG. 1. Gain of weight by eight patients on two months' or three months' treatment with isoniazid (tubercle bacilli sensitive) and with iproniazid (tubercle bacilli resistant).

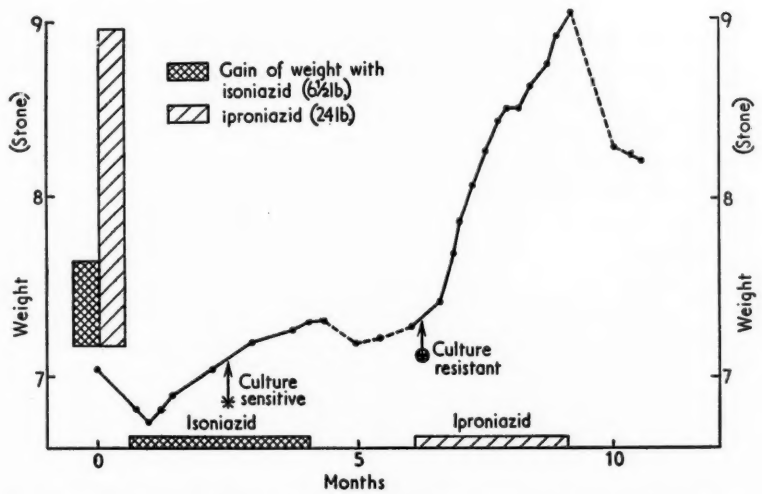


FIG. 2. The changes of weight in one patient treated with isoniazid and later with iproniazid.

the three who deteriorated in other respects, actually gained more weight with iproniazid when their bacilli were resistant than they had done with isoniazid (given in the same dose and for the same period) when their bacilli were sensitive (see Figs. 1 and 2). This indication that iproniazid may exert some specific effect upon body-weight, apart from its effect on the tubercle bacillus, has been investigated in a further series of trials, which will be reported at a later date. The second group (nine patients) treated with iproniazid in these preliminary trials had not previously received either isoniazid or iproniazid, and all were

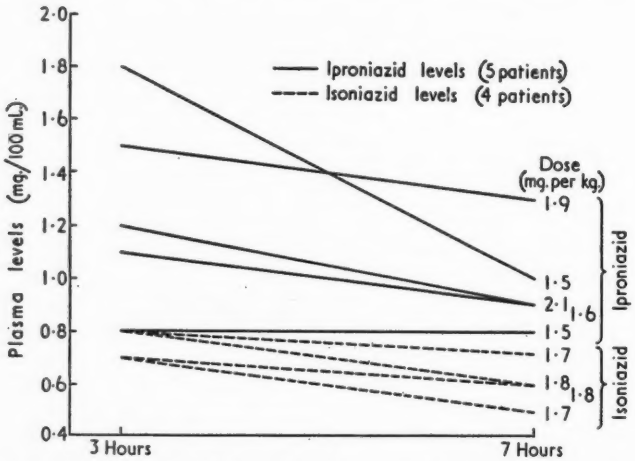


FIG. 3. Plasma levels three hours and seven hours after an oral dose of 100 mg. iproniazid or isoniazid.

yielding strains of bacilli sensitive to 0·2 μg. isoniazid per ml. Each of these patients showed clinical and radiological improvement of a similar order to that seen with isoniazid treatment, but this improvement was not sustained after the second month of treatment. Strains of bacilli resistant to 1 μg. isoniazid per ml., or more, and to equivalent concentrations of iproniazid (Ogilvie, 1954) were recovered from six of these nine patients between the seventh and twelfth weeks of iproniazid treatment. Nine of the 17 patients treated with iproniazid noticed symptoms attributable to the drug, including twitching of the limbs, hesitancy of micturition, and dizziness, but no serious toxic effects were observed. The plasma levels of isonicotinic acid hydrazide were estimated in five patients three and seven hours after an oral dose of 100 mg. iproniazid, and in four patients three and seven hours after an oral dose of 100 mg. isoniazid. The method described by Kelly and Poet (1952) was used for these estimations. Fig. 3 shows that higher plasma levels were obtained with iproniazid (mean level 1·3 μg. per ml. at three hours, 1·0 μg. per ml. at seven hours) than with isoniazid (mean level 0·75 μg. per ml. at three hours, 0·6 μg. per ml. at seven hours). It was considered that a more extensive trial of iproniazid was justified, provided that the drug was used in combination with streptomycin and that it was not given to patients yielding isoniazid-resistant strains of tubercle bacilli.

Clinical Comparison of Iproniazid and Isoniazid

A number of clinical trials of isoniazid have been described in British publications. The Medical Research Council published three papers (1952, 1953 *a*, *b*) in which the relative value of streptomycin with *p*-aminosalicylic acid, isoniazid alone, and isoniazid with streptomycin or *p*-aminosalicylic acid were compared. A small but well-designed trial, in which the effects of isoniazid alone and in combination with streptomycin were compared, has also been described by Joiner, MacLean, Chalmers, Anderson, Collard, King, and Knox (1953), at

TABLE II

Summary of Results reported by Robitzek, Selikoff, Mamlok, and Tendlau (1953)

	Isoniazid group	*Iproniazid group*
Number of patients	65	101
Temperature returned to within normal limits	79%	92%
Average gain of weight (detailed figures not given)	Increases of weight with isoniazid 'averaged half the amounts elicited with iproniazid'	
Toxic effects (detailed figures not given)	'Almost complete absence'	'Liberal incidence'
Radiological clearing	'Approximately equal benefit in the two groups'	
Cavity closure	14%	25%
Sputum conversion	25·8%	25·7%
Bacteriological resistance	Five patients studied: none resistant	14 patients studied: one resistant

Guy's Hospital. Clinical trials of iproniazid have been reported in America, and in one paper (Robitzek, Selikoff, Mamlok, and Tendlau, 1953) an attempt was made to compare the relative values of iproniazid and isoniazid. In the first account of the treatment of pulmonary tuberculosis with the hydrazine derivatives of isonicotinic acid (Robitzek, Selikoff, and Ornstein, 1952) 92 patients with extensive and bilateral caseous pneumonic disease were treated, 82 with iproniazid and 10 with isoniazid. (When the Medical Research Council, using isoniazid, subsequently reported much less striking effects than those originally described in America, it was not widely appreciated that a different drug had been used.) At a later date Robitzek, Selikoff, Mamlok, and Tendlau (1953) treated a further 19 patients with iproniazid and 55 with isoniazid, making a total of 101 in the iproniazid group and 65 in the isoniazid group. Referring to the selection of patients in the latter half of this trial, most of whom were treated with isoniazid, the authors remarked that 'with increasing experience and confidence, cases with less extensive disease were selected . . . even including a small number of cases with unilateral disease'. The authors admitted that the iproniazid group included a higher proportion of patients with advanced disease, and that this factor accounted for the higher mortality in this group (seven deaths as compared with none in the isoniazid group). The two groups were found to be comparable in regard to age, sex, race, duration of disease, and previous therapy, but other factors were not recorded. In spite of the potential and

actual differences between these two groups, the results are worth consideration in view of the comparatively large number of patients studied. The reported results at the end of two to seven months' treatment are summarized in Table II. The authors concluded that, dose for dose, the systemic effects of tuberculosis are more promptly and completely controlled by iproniazid than by isoniazid, that X-ray changes and sputum bacteriology show approximately equal benefit, and that drug toxicity is encountered more frequently and intensely with iproniazid.

Clinical Comparison of Iproniazid and Isoniazid at the London Hospital

A clinical trial designed to compare the effects of iproniazid and isoniazid upon patients with pulmonary tuberculosis was instituted in January 1953 at the London Hospital. All such patients admitted to hospital between January and October 1953 were confined to bed and subjected to a series of preliminary investigations. These included a full history and examination, a four-hourly temperature record, a chest X-ray, tomography of the affected areas of lung, estimation of the erythrocyte sedimentation rate, measurement of the daily quantity of sputum, and a microscopic and cultural examination of the sputum for tubercle bacilli. Tests for sensitivity to streptomycin and isoniazid were carried out in all patients from whom positive cultures were obtained. Each patient was seen by the physician in charge, who selected cases suitable for chemotherapy.

Treatment groups. In view of the emergence of strains resistant to iproniazid when this was given alone in our preliminary trials, it was decided to use the drug in combination with streptomycin. The régime of dosage chosen for the two treatment groups was therefore as follows:

Group I. Isoniazid, 100 mg. three times daily (at six-hourly intervals), with streptomycin, 1 gm. three times weekly.

Group II. Iproniazid, 100 mg. three times daily (at six-hourly intervals), with streptomycin, 1 gm. three times weekly.

The range of dosage of isoniazid and of iproniazid was from 4 to 8 mg. per kg. body-weight daily. Patients admitted to the trial were allotted alternately to these two groups, except the last five patients, who were all allotted to the iproniazid group in October 1953, because a high incidence of bacterial resistance had then been noted among patients in the isoniazid group.

Criteria for admission to the trial. (1) Each patient had been considered suitable for chemotherapy by the physician in charge. (2) No patient had previously received isoniazid or iproniazid, or more than a total dose of 20 gm. of streptomycin. (3) Tubercle bacilli had been recovered from a specimen of sputum collected within one week of the start of treatment. (4) The bacilli were sensitive to a concentration of 0·2 μg. per ml. isoniazid and 3 μg. per ml. streptomycin. It was necessary to apply the fourth criterion retrospectively, but resistant strains were not, in fact, recovered from the sputum specimen taken before treatment from any patient admitted to the trial. The third criterion was also applied retrospectively to 16 patients whose sputum was negative on direct

examination when admitted to the trial. The sputum from 12 of these patients proved to be positive on culture, the remaining four being negative. These four patients (three in the isoniazid group and one in the iproniazid group) were therefore withdrawn from the trial. Another patient in the iproniazid group was also withdrawn because of the side-effects of the drug. Between January and October, 1953, 27 patients were admitted to the isoniazid group and 32 to the iproniazid group. As already stated, three of the former and two of the latter were withdrawn, leaving a total of 24 in the isoniazid group and 30 in the iproniazid group.

Period of treatment and observation. Previous experience at the London Hospital had shown that whereas streptomycin, given twice or thrice weekly, would delay isoniazid resistance for three months, there was a high incidence of resistance in the fourth month of treatment. It was then decided that surgical or collapse therapy should be instituted, whenever practicable, during the third month of chemotherapy, so that effective 'cover' would still be available. This meant that the number of patients having chemotherapy as the sole mode of treatment for longer than two months would not be sufficient for the purposes of this trial. It was therefore decided that the progress of the two trial groups should be assessed at the end of a two-month period, but that observations upon the incidence of side-effects and the emergence of resistant strains could reasonably be continued after physical modes of treatment had been instituted.

Method of assessment. All patients were confined to bed, and no antituberculous treatment other than the prescribed régime of chemotherapy given, during the first two months of treatment. The preliminary investigations enumerated in the first paragraph of this section were completed before drug treatment was started. The following investigations were carried out during the two-month period of observation: (1) *Daily*: four-hourly temperature chart; measurement of sputum volume. (2) *Three times weekly*: urine examination for albumin and sugar. (3) *Weekly*: record of weight. (4) *Monthly*: chest X-ray; sputum microscopy and culture for tubercle bacilli; tests for isoniazid and streptomycin sensitivity; estimation of erythrocyte sedimentation rate. (5) Tomograms were taken before treatment, and again at the end of two months, if no cavities were visible in the original direct film. Tests for isoniazid and streptomycin sensitivity were carried out at monthly intervals during the whole period of drug treatment (three to four months). A record of side-effects was also kept during this period, and such effects were also noted in a separate group of patients being treated with isoniazid or iproniazid for extrapulmonary tuberculous lesions.

The condition of the patients before treatment. The majority of patients in both treatment groups fell into Group II of the Medical Research Council's classification (1952). These patients were all suffering from recent disease (not acute and rapidly progressive) or from chronic disease with recent spread. Two patients in the iproniazid group and one in the isoniazid group had acute and rapidly progressive disease of recent origin (Medical Research Council, Group I). Five patients in the iproniazid group and three in the isoniazid group were classified

as cases of chronic disease expected to make only a limited response to chemotherapy (Medical Research Council, Group III). The assessment of the condition of patients in the two groups before treatment is summarized in Table III. It is

TABLE III

Condition of Patients in the Two Groups Before Treatment

	Group I (isoniazid)	*Group II (iproniazid)*
Total number of patients	24	30
Sex: male	11 (46%)	13 (43%)
female	13 (54%)	17 (57%)
Average age	37·5 years	37 years
Average duration of present illness	5·4 months (plus one case of over two years' continuous illness)	5 months (plus three cases of over two years' continuous illness)
Probable duration of disease:		
No symptoms or X-ray evidence of pulmonary tuberculosis previous to present illness	15 patients (62·5%)	17 patients (57%)
Symptoms or X-ray evidence of pulmonary tuberculosis more than two years before present illness	9 patients (37·5%)	13 patients (43%)
Physical signs of exudation or consolidation	17 patients (70%)	18 patients (60%)
Fever (readings of over 100° F. on at least three days prior to treatment)	6 patients (25%)	5 patients (17%)
Average body-weight	122 lb.	124 lb.
Average of patients' normal weights	132 lb.	133 lb.
Sputum:		
Number of patients with a measurable volume (over 8 drachms per day)	7 (29%)	9 (30%)
Number positive on direct smear	19 (79%)	23 (77%)
Number positive on culture only	5 (21%)	7 (23%)
Average rate of erythrocyte sedimentation	42 mm. in one hour	38 mm. in one hour
Haemoglobin level (average of 13 cases in each group)	80%	78%
Radiographic findings:		
Total number of lung zones involved	63 (average of 2·6 zones per patient)	85 (average of 2·8 zones per patient)
Unilateral disease	12 patients (50%)	12 patients (40%)
Bilateral disease	12 patients (50%)	18 patients (60%)
Cavitation:		
None	8 patients (33%)	11 patients (37%)
Single	8 patients (33%)	10 patients (33%)
Multiple	8 patients (33%)	9 patients (30%)
Large cavities (over 1 inch diameter)	11 patients (46%)	12 patients (40%)

seen that there are no significant differences between the iproniazid and isoniazid groups in regard to the factors considered.

Results

Symptomatic improvement was difficult to assess accurately. The improvement in appetite, sense of well-being, and general nutrition was more striking in the

iproniazid group, but was associated with evidence of euphoria in a number of these patients.

Fever. The five febrile patients in the iproniazid group lost their fever within 12 days of starting treatment. Three of the six febrile patients in the isoniazid group lost their fever after seven days, while in three it persisted throughout the two months of observation.

Weight. The average gain of weight in two months was 7·6 lb. in the isoniazid group and 14·4 lb. in the iproniazid group. Table IV shows that 19 iproniazid

TABLE IV

Changes of Weight in Two Months

	Total number of patients	*Gain*				*Loss*
		over 21 lb.	*15–21 lb.*	*8–14 lb.*	*0–7 lb.*	
Isoniazid group	24	2	2	7	12	1
Iproniazid group	30	6	13	6	5	0

TABLE V

Changes in the Erythrocyte Sedimentation Rate in Two Months

	Total number of patients		*E.S.R. (mm. in 1 hour)*			
			0–20	*21–30*	*31–50*	*51 and over*
Isoniazid group	24	Before treatment	5	8	3	8
		After two months	15	2	6	1
Iproniazid group	30	Before treatment	12	2	6	10
		After two months	22	4	0	4

patients gained more than one stone in weight, as compared with four isoniazid patients. Five iproniazid patients gained less than half a stone, as compared with 13 isoniazid patients.

Sputum. The volume of sputum was reduced to less than eight drachms per day in five of seven isoniazid patients (29 per cent.) and in six of nine iproniazid patients (30 per cent.). At the end of two months' treatment three consecutive daily samples of sputum were negative on direct examination and culture in 12 iproniazid patients (40 per cent.), and in nine isoniazid patients (37·5 per cent.). The sputum was negative on direct examination but positive on culture in one patient from each group.

Erythrocyte sedimentation rate (*E.S.R.*). The distribution of the sedimentation rates before and after two months' treatment is shown in Table V. Before treatment there was a relatively greater number of iproniazid patients in the 0–20 mm. range, and a relatively greater number of isoniazid patients in the 21–30 mm. range. Otherwise the distribution in the two groups was approximately equal. The E.S.R. fell from an average of 38 mm. to 21·5 mm. in the iproniazid group, and from 42 mm. to 23 mm. in the isoniazid group. If the patients with an initial E.S.R. of over 20 mm. are considered, the average fall in two months was 29 mm. in the iproniazid group and 22 mm. in the isoniazid group. Of 18 patients with an initial E.S.R. of over 20 mm. in the iproniazid group, seven had an E.S.R. of less than 10 mm. after two months' treatment.

Of 19 patients with an initial E.S.R. of over 20 mm. in the isoniazid group five had an E.S.R. of less than 10 mm. after two months' treatment.

Radiographic changes. In the two-month period of chemotherapy, improvement as judged by diminution in the extent of radiological shadowing was of too slight a degree to allow a reliable comparison between the two treatment groups. Twenty-one isoniazid patients (87 per cent.) and 24 iproniazid patients (80 per cent.) showed some radiological clearing, but in only one patient from each group was this change considered to be striking. Deterioration was not observed in either group. Changes in the size of cavities were more easy to assess. There was a decrease in the size of one or more cavities in 17 of 18 iproniazid patients (94 per cent.) and in 11 of 14 isoniazid patients (78 per cent.). The closure of a large cavity (more than one inch in diameter) was observed and confirmed by tomography in two of 11 isoniazid patients (18 per cent.) and in six of 12 iproniazid patients (50 per cent.). One patient in the isoniazid group showed an increase in the size of a cavity.

Sensitivity to isoniazid and streptomycin. The methods used for determining bacteriological sensitivity to isoniazid, iproniazid, and streptomycin, and a preliminary account of the results obtained in these trials, have already been reported (Ogilvie, 1954). Sensitivity tests were carried out on the sputum of all patients yielding positive cultures at the end of each month of treatment, and were continued until chemotherapy was withdrawn. Isoniazid-resistant strains were not recovered from patients in either group during the first two months of treatment. In the isoniazid group, four of eight patients completing four months' treatment yielded strains resistant to isoniazid, the bacilli in three cases being resistant to 50 μg. per ml. (the highest concentration used) and in one case to 1 μg. per ml. Two of these four patients first yielded resistant strains after only three months' treatment. In the iproniazid group, on the other hand, 12 patients completing three months' treatment and eight completing four months' treatment all yielded strains sensitive to 0·2 μg. per ml. isoniazid and to equivalent concentrations of iproniazid. None of the patients in either group yielded strains resistant to 3 μg. per ml. streptomycin at any stage of treatment (including the four patients who yielded isoniazid-resistant strains).

An analysis of the status, before treatment, of patients for whom sensitivity results were available in the fourth month of treatment, did not reveal any significant differences between the isoniazid and iproniazid groups as regards duration, type and activity of the disease, or extent of lung cavitation. It is also unlikely that the incidence of bacterial resistance was influenced by physical modes of treatment adopted in the third month: an artificial pneumothorax had been induced in two patients in the iproniazid group, and in one of the patients in the isoniazid group whose bacilli were resistant. A phrenic crush had been performed in one of the isoniazid patients whose bacilli were sensitive.

Toxic effects. The study of toxic effects was extended to include a group of patients with extrapulmonary tuberculosis. Twenty-three of these patients were under treatment with isoniazid and 12 with iproniazid, both drugs being given in the same dose as in the main trial. The total number of patients under

observation was therefore 47 in the isoniazid group and 42 in the iproniazid group. A record of the toxic effects in each group was kept for a period of three months. The incidence of symptoms considered to be attributable to the drug used is recorded in Table VI. A detailed account of these symptoms will be reported at a later date. The incidence of toxic effects was considerably greater in the iproniazid than in the isoniazid group: 35 iproniazid patients (83 per cent.)

TABLE VI

Toxic Effects

Symptoms	*Number of patients affected*	
	Iproniazid group (42 patients under observation)	*Isoniazid group* (47 patients under observation)
Twitching of limbs and exaggerated reflexes	30	4
Hesitancy of micturition	18	3
Headaches	12	5
Insomnia	10	0
Dizziness	8	2
Hypotension	6	0
Drowsiness	5	3
Attacks of severe headache associated with palpitations, flushes, sweats, and raised blood-pressure	4	0
Blurred vision	3	1
Nightmares	3	0
Severe constipation	3	1
Acute retention of urine	3	0
Frequency and nocturia	2	0
Confusional psychosis	2	0
Febrile reaction	1	0
Paraesthesiae	1	0
Jaundice	1	0
'Withdrawal' symptoms	17 (30 under observation)	3 (27 under observation)

and 16 isoniazid patients (34 per cent.) complained of symptoms attributable to the drug used. In the iproniazid group there was an average of between two and three symptoms of drug toxicity per patient, and in the isoniazid group one symptom for every two to three patients. Eighteen different symptoms were noted in the iproniazid group and seven in the isoniazid group. During the month after chemotherapy was discontinued, 17 of 30 iproniazid patients studied and three of 27 isoniazid patients complained of 'withdrawal' symptoms similar to those described by Selikoff, Robitzek, and Ornstein (1953). Depression, irritability, and nightmares were the symptoms most frequently encountered.

Discussion

It is notoriously difficult to ensure that any two groups of patients with pulmonary tuberculosis are comparable for the purpose of assessing the efficacy of different modes of treatment. This can best be achieved by the random allocation of large numbers of patients to the two groups over the same period of time. In the American trial of iproniazid and isoniazid (Robitzek, Selikoff, Mamlok, and Tendlau, 1953) a comparatively large number of patients was

studied, but the main allocation to each treatment group occurred at different times; the criteria for the admission of patients to the earlier group (mainly iproniazid) were not the same as for the later group (mainly isoniazid). In the present study patients were first selected as suitable for the trial, and were then allotted alternately to the two treatment groups over approximately the same period of time; the total number of patients in each group, however, was comparatively small. Any conclusions which may be drawn from the results of our

TABLE VII

Analysis of Results in the Two Treatment Groups

The total number of patients from whom the information is derived in each section is indicated in parentheses.

	Loss of fever within two weeks	*Average gain of weight in two months*	*Sputum conversion in two months*	*Erythrocyte sedimentation rate initially above 20 mm. in one hr.: average reduction in two months (mm./hr.)*	*Radiological clearing in two months*	*Closure of large cavities in two months*	*Bacteriologically sensitive at 100 days*	*Toxic effects during three months*
Isoniazid group	50% (6 patients)	7·6 lb. (24 patients)	37·5% (24 patients)	22 (19 patients)	87% (24 patients)	18% (11 patients)	50% (8 patients)	34% (47 patients)
Iproniazid group	100% (5 patients)	14·4 lb. (30 patients)	40% (30 patients)	29 (18 patients)	80% (30 patients)	50% (12 patients)	100% (8 patients)	83% (42 patients)

trial are, for the most part, applicable to the treatment of patients with recent disease, or a recent exacerbation of chronic disease, over a two-month period (and over a three-month period in the case of bacterial sensitivity and toxic effects). In the final analysis (Table VII) it is seen that there is a considerable difference between the iproniazid and isoniazid groups in regard to average gain of weight and the incidence of toxic effects. The average gain of weight in the iproniazid group was nearly twice that found in the isoniazid group, and toxic effects were experienced by two and a half times as many patients in the iproniazid group as in the isoniazid group. Temperature response, the closure of large cavities, and the incidence of bacteriological resistance were more favourable in the iproniazid group, but the number of patients observed was too small to make these differences more than suggestive. Symptomatic improvement was also more striking with iproniazid, but may have been related to the euphoric effect of this drug. Sputum conversion, radiological clearing, and fall in the erythrocyte sedimentation rate were of a similar order in the two groups. It is of some interest that, although there were considerable differences in the design and duration of the two trials and in the type of case treated, the American results were similar to those obtained in the present study (see Tables II and VII). It is, however, remarkable that little evidence of resistance to isoniazid or iproniazid was found by the American workers, considering that streptomycin was not used in either treatment group. During an average period of 112 days only one patient (in the iproniazid group) yielded resistant strains. This result is at variance with the findings in subsequent trials of isoniazid (Medical Research Council, 1952; Joiner, MacLean, Chalmers, Anderson, Col-

lard, King, and Knox, 1953) and of iproniazid (Nash and Grosfeld, 1952) (see also the preliminary studies recorded in the present paper).

It was noted in our preliminary trials that the plasma levels of isonicotinic acid hydrazide after an oral dose of 100 mg. of iproniazid were approximately twice those found after the same dose of isoniazid. Lewis (1952) also reported that plasma levels of iproniazid were higher and better sustained than those of isoniazid. Robitzek, Selikoff, Mamlok, and Tendlau (1953) pointed out that the higher plasma levels attained might be responsible for the better progress of their group of patients treated with iproniazid. They suggested that until the optimum dosage of isoniazid had been determined a proper comparison between iproniazid and isoniazid would not be possible. This last observation must be accepted, for it has yet to be shown that higher doses of isoniazid than those used in the American trial and in our own (4 to 8 mg. per kg. body-weight in both trials) might not have produced a greater clinical response without serious toxic effects. This criticism must necessarily apply also to trials in which isoniazid and streptomycin have been compared; in the original Medical Research Council trial (1952), for instance, a standard dose of only 200 mg. isoniazid (one-third less than the dose used in the present study) was employed.

The higher plasma levels in iproniazid may well account for the greater incidence of toxic effects in patients treated with this drug. It seems unlikely, however, that the differences in the plasma levels of isoniazid and iproniazid are sufficient to offset the fact that iproniazid is about 60 times less active than isoniazid against the tubercle bacillus *in vitro*. Why, then, should patients treated with iproniazid progress at least as well, and also gain considerably more weight, than those treated with isoniazid? I have reported earlier in this paper that patients with bacteriologically resistant infections gained more weight with iproniazid than they had done with isoniazid when their bacilli were sensitive. Further trials at the London Hospital (Ogilvie, 1953) show that the gain in weight of tuberculous patients treated with iproniazid cannot be directly correlated with the initial severity or the progress of the disease, and that iproniazid can also induce an increase in the weight of certain non-tuberculous subjects. Gains of weight were found to be commensurate with increased intake of food, and could be abolished by a restriction of the diet. Evidence that iproniazid may increase body-weight and improve the general nutrition of non-tuberculous subjects has also been offered by Bosworth (1952), Fisher, Mamlok, Tendlau, Tebrock, and Spiegelman (1952), and Smith (1953), but similar results have not been obtained with isoniazid (Mudie, Horne, and Crofton, 1954). We have concluded that iproniazid exerts some specific effect upon appetite, and thus upon general nutrition, quite apart from its anti-tuberculous properties, and that this factor may have contributed to the relatively favourable progress of our group of patients treated with iproniazid.

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Summary

The known differences between iproniazid and isoniazid are summarized, and the higher plasma levels of iproniazid which can be attained in man are confirmed.

Iproniazid is shown to be ineffective against tuberculous infections resistant to isoniazid, but effective against sensitive infections. The emergence of resistant strains was noted in a high proportion of patients treated with iproniazid alone.

Two comparable groups of patients with pulmonary tuberculosis (mainly recent disease, or a recent spread of chronic disease) have been treated for two to four months with iproniazid and isoniazid respectively, each drug being combined with streptomycin. Average gains of weight, and the incidence of toxic effects, were considerably greater in the group treated with iproniazid. Progress, as judged by temperature response, the closure of large cavities, and the incidence of bacteriological resistance, was more favourable in the iproniazid group.

It is suggested that the higher plasma levels of iproniazid were responsible for some of the differences observed, but are unlikely to have offset the much poorer bacteriostatic properties of this drug; a specific increase in appetite may have contributed to the relatively favourable progress of patients treated with iproniazid.

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HEART FAILURE IN INFANCY WITH ABNORMALITIES OF THE VALVES AND ENDOCARDIUM[1]

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With Plates 14 to 18

Cardiac failure in infancy is not very uncommon, but the early symptoms and the physical signs are probably often misinterpreted. Failure may occur in episodes of paroxysmal tachycardia, or more rarely in acute myocarditis. Glycogen-storage cardiomegaly and myocardial rhabdomyomatosis are still rarer causes, and there are few recorded cases of rheumatic heart disease occurring in the first year of life. The commonest cause is congenital heart disease, which tends to be of a type—not well defined—involving the endocardium, chiefly on the left side of the heart, and one or more valves, and which may be associated with certain other cardiovascular abnormalities, especially patency of the ductus arteriosus. A number of cases and series of cases of this type have been reported during the last few years under the heading of endocardial sclerosis, fibrosis, or fibroelastosis. Three such cases have come under our observation during the last year. The present paper consists of a study of these cases and the diagnostic difficulties which they have seemed to illustrate, a review of some previous reports, and a discussion of the problems of aetiology and pathogenesis. Finally the prognosis, the possibilities of treatment, and the probable incidence of such cases are considered.

Case Reports

Case 1. Jane S., the only child of healthy parents, was born on February 2, 1953, after a normal pregnancy, in the Canadian Hospital. Establishment of feeding was difficult, and on discharge at the age of two weeks she weighed one ounce less than at birth. She was examined on discharge, and no abnormality was found in the cardiovascular system or elsewhere. Her mother brought her up to the out-patient clinic 10 days after her return home, with the story that she had seemed fretful and feverish for a few days. On examination she was found to have an infected umbilical stump, with a brownish purulent discharge; her temperature was 101°F., and she looked ill; there was slight oedema of the legs, and the edge of the liver was unduly easily palpable. She was admitted to the ward and given oral penicillin, a swab having been taken from the umbilicus. Lactation had failed on the mother's return home from hospital, and the baby was now bottle-fed. After admission the signs of infection cleared up rapidly, and her general condition improved. Feeding, however, was again found to be difficult, and she had several choking attacks, in one of which it

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was feared that part of the feed might have been inhaled. On going into this matter more carefully, a few days after admission, it was found that the real feeding difficulty was an effort dyspnoea, with an increase in respiratory rate up to 70 or 80 about half-way through the feed. It was also at this time noticed that the liver was enlarged, the edge being felt two inches below the costal margin, and that râles were audible over both lung fields. The heart sounds were normal, with no murmurs, the rate varying from 90 to 140. The blood-pressure was 80/60; the femoral pulses were normal; X-rays showed a somewhat globular and probably enlarged heart shadow (Plate 15, Fig. 8); an electro-cardiogram showed no abnormality. It was apparent that she was in cardiac failure, and she was given digoxin 0·025 mg. six-hourly; rapid improvement followed, the symptoms and signs of failure disappearing completely within six days. Feeds were now taken well with no distress, and she gained weight steadily. Three weeks after admission signs of failure reappeared, the liver edge again descending, and râles becoming audible as her respiratory rate rose. There was some oedema of the legs and sacral region. At this time a soft apical systolic murmur became audible. Digoxin was increased to 0·05 mg. six-hourly, again with rapid disappearance of physical signs, and on discharge she was well, taking full feeds satisfactorily, and receiving digoxin 0·1 mg. twice daily. She remained under supervision as an out-patient until, at the age of four months, she again showed symptoms, and the dose of digoxin was further increased to 0·125 mg. twice daily. She improved rapidly as on the previous occasion, but at the age of five months, after a cold, was admitted with severe failure. The systolic murmur, first heard at six weeks, was now much louder and was audible all over the chest, being loudest at the region of the apex beat; at this time a diastolic murmur was first heard in the mitral area, and was constantly present thereafter. Antibiotics were given, and digoxin was further increased to 0·15 mg. twice daily. Improvement this time was slower, but on discharge a month after this admission she seemed fairly well, though gain of weight had been slow; there were no signs of failure. At the time of her final admission to hospital, at the age of seven months, it was at once apparent that her condition was deteriorating: there was continuous respiratory distress, and feeding was increasingly difficult. On increasing the dose of digoxin to 0·175 mg. twice daily, enlargement of the liver and oedema again regressed, and her respiratory rate fell, but this improvement lasted only for a few days. She was febrile and took very little food in the last ten days of her life. In the month before she died, aged nearly eight months, the systolic murmur became still louder and was accompanied by a thrill, and the diastolic murmur became a typical mitral rumble. Serial electrocardiograms showed a varying digitalis effect, lengthening of the P–R interval amounting to first-degree block, and on one occasion, at the maximum dosage, a short period of 2:1 auriculo-ventricular block in one tracing. Gradually deepening Q-waves and the development of high 'pulmonary' P-waves were also shown (Fig. 1). The blood picture and the urine were normal on several occasions. The plasma-proteins, estimated at seven months, were normal. It was thought that this child had endocardial fibroelastosis, and later, when the murmurs were heard, that there probably was involvement of the mitral valve with stenosis and incompetence.

Post-mortem findings. The appearances were those of cardiac failure with congestion. There were no structural abnormalities apart from the cardio-vascular system and lungs. The latter, in addition to gross congestion, showed patchy areas of collapse. There was some muco-pus in the trachea, but the bronchi were patent. A few petechiae were seen in the visceral pleura of both

lungs. The heart was considerably enlarged, and weighed 85 gm. Both ventricles were hypertrophied, especially the left. The myocardium and pericardium were macroscopically normal, but the endocardium of the left auricle and ventricle (Plate 14, Fig. 3) was distinctly thickened and opaque. A similar thickening of the right ventricular endocardium was less marked, and was limited to the basal portion. The pulmonary and aortic valves were normal, but the

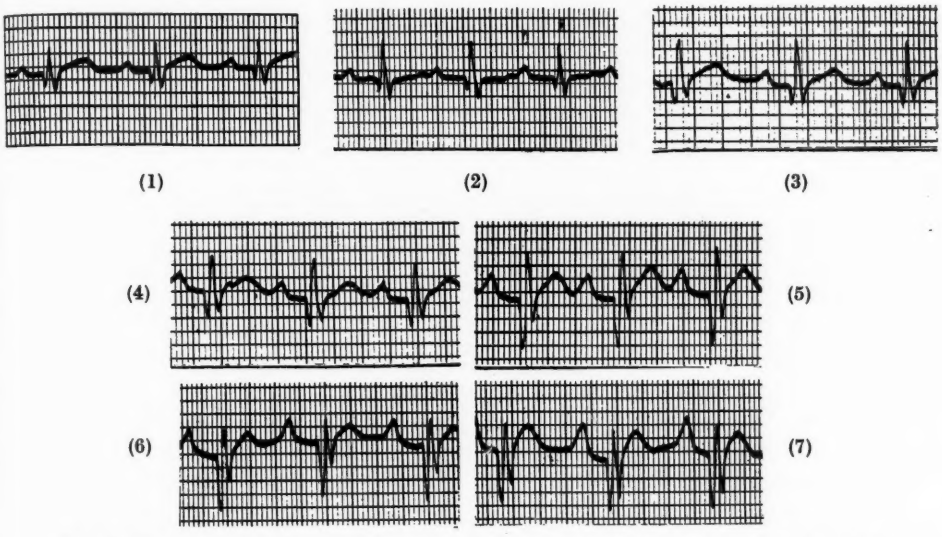

FIG. 1. Case 1. Serial electrocardiographic tracings (standard lead II), from the age of one month to that of seven months, showing gradual development of Q-waves and high P-waves.

mitral and tricuspid valves were much thickened and abnormally translucent. The chordae of the mitral valve were thickened, and their arrangement and insertion into the cusps distorted. The thickened and abnormally shaped mitral cusps were partly adherent to each other, so that there was gross incompetence and slight stenosis (Plate 14, Fig. 4). The foramen ovale and the ductus arteriosus were closed.

Histology. Sections of the lungs confirmed the presence of intense congestion, oedema, and areas of collapse, and there were many intra-alveolar phagocytes. The pulmonary arterioles and other vessels were normal. The liver showed the characteristic appearances of prolonged congestion. The myocardium appeared normal. The endocardium of the left ventricle, both on the septum and on the lateral wall, was several times the normal thickness, and rich in elastic and collagen fibres (Plate 14, Fig. 5). Several bundles of myocardial fibres were lying embedded within this fibroelastic layer. The thickness of the left auricular endocardium was grossly exaggerated, and in places was more than twice that of the auricular muscle layer (Plate 15, Fig. 6). Sections of both mitral and tricuspid valves showed much increased fibrosis and myxoma-like thickening. In both cases there was a small area of calcification in the valve ring, and a similar but minute focus was found in the aortic ring. There was no evidence of any inflammatory cell infiltration either in the mural endocardium or in any of the valve sections (Plate 15, Fig. 7).

Case 2. Linda A., born March 23, 1953, the youngest of five children, was brought to the Children's Clinic at the Royal Berkshire Hospital by the Children's Officer. Home conditions were extremely bad, and the baby was thought to be suffering from neglect. Her weight at five months was 10 lb. 10 oz., the birth weight having been 9 lb. No very coherent history was obtainable from the mother, but it seemed that occasional vomiting, and also episodes of breathlessness and choking during feeds, had occurred from birth. On examination she was a thin, ill-looking baby. The respiratory rate was 60, with no pyrexia and a heart rate of 100. She was in cardiac failure, with very slight oedema

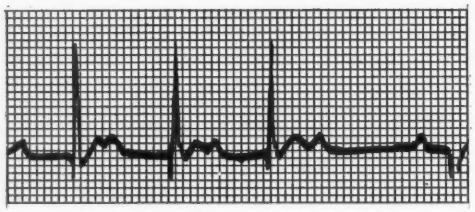

FIG. 2. Case 2. Electrocardiogram (standard lead II) showing auriculo-ventricular dissociation after treatment for a week with digoxin 0·05 mg. twice daily.

of the legs and back, enlargement of the liver to below the level of the umbilicus, and râles heard behind over the lungs. There was no cyanosis. A soft systolic murmur was audible over the cardiac apex, and a low-pitched rumbling diastolic murmur was heard in the mitral area. The systolic blood-pressure was 110 mm. Hg. but no diastolic level could be measured, the sounds remaining unchanged to zero. The femoral pulses were easily felt and were collapsing in character. There was some visible pulsation in the neck. X-rays showed an enlarged heart, with increase in the width of the shadow of the superior mediastinum, and pronounced vascular marking in the lung fields. There was collapse of the right middle lobe (Plate 17, Fig. 11). The electrocardiogram, urine, and blood picture were normal. She was admitted to hospital and digoxin was given, but this produced no improvement, and signs of failure persisted. A further electrocardiogram, after digoxin 0·05 mg. twice daily for a week, showed auriculo-ventricular dissociation (Fig. 2). She deteriorated steadily in hospital, and died three weeks after admission. This case was thought to be similar to the previous one, the process again involving the mitral valve.

Post-mortem findings. Apart from the appearances of congestion, abnormal findings were limited to the lungs and cardiovascular system. The lungs showed oedema, congestion, and patchy areas of hyperaemia and collapse; the right middle lobe was completely collapsed. The heart was enlarged and weighed 89 gm., the enlargement being mainly due to hypertrophy of the left ventricle. The myocardium appeared normal, but the endocardium of the left auricle was markedly thickened; the same white pearly thickening was present in the left ventricular endocardium, especially on the septal wall near the base. Both mitral and tricuspid orifices were reduced in size, the valve cusps being thickened and deformed and the chordae extremely distorted in shape and arrangement (Plate 16, Figs. 9 and 10). The pulmonary valve was normal, but the aortic valve was bicuspid owing to fusion of the non-coronary and the right coronary cusps. There was a small defect in the

membranous part of the interventricular septum. The foramen ovale was completely closed, but the ductus arteriosus was widely patent.

Histology. Lung sections showed congestion, oedema, and numerous 'heart-failure' cells containing haemosiderin. The pulmonary vessels were normal. Sections of the thickened areas in the left ventricular (Plate 17, Fig. 12) and left auricular walls showed an appearance similar to that seen in the previous case, as did sections of the abnormal valves. As before, there was no evidence in any of these sections of inflammatory changes.

Case 3. Susan H., born June 18, 1953, was the first live baby of healthy parents. There had previously been a still-birth and a miscarriage, and the still-born baby was said to have had an enlarged heart. The parents had attended a fertility clinic, and the mother had had a progesterone implant during pregnancy. No illness occurred during the pregnancy, and normal delivery took place at full term at the Canadian Hospital. At the age of two days the baby choked over a feed and became blue. It was thought that some feed might have been inhaled, and penicillin was given orally for four days. She appeared to be normal in all respects, and had regained her birth weight, when she was examined on discharge at the age of 14 days; but breathlessness during feeds continued to occur at home, though not to a severe extent. At the age of four months she was examined by the doctor who vaccinated her, and a systolic murmur was noticed. Three weeks after vaccination she was again seen by the doctor, because she seemed breathless for no apparent reason and was now exhausted by feeding. She was sent into hospital with these symptoms, and was found on admission to be in cardiac failure. There was no pyrexia; her heart rate was 140, with a respiratory rate at rest of 40–60. The edge of the liver was felt two inches below the costal margin. There was slight sacral oedema. Râles were audible over the lungs behind. The blood-pressure was 90/40, but the figures varied considerably, and diastolic levels down to 20 mm. were recorded. It was thought that the pulse was somewhat collapsing in type, and that pulsation of the femoral artery could be felt unusually easily. There was no abnormal visible pulsation in the neck, but it was thought on one occasion that pulsation could be felt in the liver. A systolic murmur was audible at the apex and also at the base of the heart. The basal murmur was loudest to the right of the sternum, and could also be heard above the right clavicle. An enlarged heart shadow, with widening of the superior mediastinum and engorgement of the lung fields, was seen on X-ray (Plate 17, Fig. 13). An electrocardiogram showed no abnormality. The blood picture and urine were normal. After admission to hospital there was considerable improvement. Digoxin was given with an initial dosage of 0·125 mg. eight-hourly for three doses, and then a smaller dose of 0·075 mg. daily; this maintenance dose was later increased to 0·125 mg. daily. For some weeks it seemed that improvement was maintained. Further electrocardiograms showed slight ST deviation, which may have been due to digitalis, but no other changes. In spite of improvement in physical signs—her liver was no longer palpably enlarged—she was never quite free from some respiratory distress, and her respiratory rate rarely fell below 40. She collapsed suddenly after a feed and died six weeks after admission, at the age of five and a half months. A diastolic murmur had become audible in the mitral area in the last week of life. There were no further notable electrocardiographic changes. This case was thought to be similar to the previous one with, in view of the basal murmur and high pulse-pressure, involvement of the aortic valve and possibly a patent ductus arteriosus.

Post-mortem findings. Apart from the appearances of very marked congestion

the only abnormal findings were in the heart, which was enlarged and weighed 67 gm., the enlargement being due to hypertrophy of both ventricles. The aortic valve was bicuspid owing to fusion of the two coronary cusps (Plate 18, Fig. 14). The mitral and pulmonary valves were normal, but the tricuspid valve was grossly thickened and deformed, the septal cusp being almost fixed to the ventricular wall by abnormally thick short chordae and the valve as a whole being obviously incompetent (Plate 18, Fig. 15). The endocardium of both ventricles showed opaque thickening, more marked on the right. The foramen ovale was closed, and the ductus arteriosus widely patent.

Histology. The endocardium of both ventricles showed thickening of the same type as in the previous cases. Several clumps of myocardial fibres were seen within the thickened septal endocardial layer on both sides of the septum. The tricuspid valve showed myxomatous thickening, and the same appearance was found to a very much smaller extent in a section of the mitral valve, which had appeared macroscopically normal or at least not significantly thickened. The aortic and pulmonary valves were histologically normal. Lung and liver sections showed appearances similar to those seen in the previous two cases.

Discussion

These three babies died in cardiac failure, the symptoms and signs of which were in each case misinterpreted or only recognized relatively late in the illness. This circumstance has seemed to us a sufficient reason for detailed study of their cases, particularly as in almost all recorded cases, observed during life, in which this type of heart abnormality has been found, the infant has presented similar symptoms and signs. These, the more chronic manifestations of failure, are easily recognized in the adult with heart disease in whom they are expected, but are unfamiliar in infancy. Even when the possibility is borne in mind the diagnosis may be very difficult. Breathlessness, an effort dyspnoea, is the most frequent first symptom. The respiratory rate rises with the effort of sucking, and a choking fit occurs which may be regarded as due to a technical feeding error. Later the increased respiratory rate at rest, with râles audible over the lungs, is likely to be attributed to chest infection, especially as infection often seems in fact to precipitate an episode of failure, just as it may in the adult. The paroxysmal or episodic nature of the breathlessness may, however, suggest a cardiac origin before signs of congestion appear, especially if the child can be observed for fairly long periods. Pyrexia tends to be an unreliable sign in early infancy. Acute pneumonia in the absence of heart disease does not, of course, lead to cardiac failure, the terminal picture in fatal cases being one of shock or peripheral vascular failure. Pneumonia and cardiac failure may, however, occur together, and—further to complicate the diagnostic problem presented by these babies—the inhalation, resulting from cardiac dyspnoea, of part of a feed may lead in turn to a segmental or more extensive pneumonic consolidation. Enlargement of the liver is the first unequivocal sign, but even this can present considerable difficulty. The edge of the liver in small babies is normally palpable near the costal margin, and a slight degree of enlargement may easily escape notice, while very careful palpation in an adequately relaxed abdomen may be necessary in order to feel the soft diffuse enlargement of this organ,

which sometimes in cardiac failure extends well below the umbilicus. Venous congestion in the neck seems to be a sign of little value in infants. Oedema may be slight or absent. Cyanosis may be absent or may only occur terminally.

Heart murmurs are usually considered to be of little diagnostic value in this type of case, though in the present three cases they seemed significant. Mitral valve disease can certainly occur in infancy without typical murmurs, as can a persistently patent ductus. Measurement of blood-pressure is of obvious importance: the high pulse-pressure in Case 2, together with the radiological appearances, might well have indicated a patent ductus arteriosus, and in Case 3, which occurred soon after the autopsy on Case 2, the diagnosis could tentatively be made. Radiologically a characteristic globular enlargement of the heart has been reported by various authors, and is well shown in Case 1. This appearance perhaps indicates involvement of the left ventricular mural endocardium. The widening of the basal cardiac shadow and the upper mediastinum, with engorgement of the lung fields, when the ductus is functionally patent, is shown in Cases 2 and 3.

A number of reviews of similar cases have appeared in the last few years. Blumberg and Lyon (1952) described a series of 25 cases of endocardial sclerosis confirmed by autopsy, all the patients dying in infancy or early childhood. Valve involvement was noted in nine cases, and in five the ductus arteriosus was patent. In two there was coarctation of the aorta. Dennis, Hansen, and Corpening (1953) reviewed 149 previously recorded cases in which autopsy reports were available; of these children two were still-born, 111 died during the first year, 29 survived for periods of one to six and a half years, and one died at 11½ years of age; the age at death was not known in six cases. There were valve deformities in 68 of the 131 cases in which the valves were described. The aortic and mitral valves were most frequently involved, and the mural and valve abnormalities were limited to the left side of the heart in 82 per cent. of the cases. There was no difference in sex incidence. No note was made of associated cardiovascular abnormalities, but the two cases reported by Blumberg and Lyon in which coarctation was found were excluded for this reason. Gowing (1953) described three cases which came to autopsy, and reviewed the literature. Two of his patients were seen because of early feeding difficulty, and the third on account of bronchitis at two months, which failed to respond to treatment. Craig (1949), in a review of autopsy material in the Boston Children's Hospital from 1928 to 1948, and at the Boston Lying-in Hospital from 1932 to 1949, reported 43 cases. In 11 cases the mural endocardium alone was involved, and in 26 both the wall and one or more valves. In six cases the process was limited to valves. The great majority of lesions were on the left side of the heart. The ductus arteriosus was patent in 10 cases; the ages at death were in one case 13 days, in four cases two months, in three between four and eleven months, and in one four and a half years.

The reported figures thus suggest that valve involvement occurs in from one-third to one-half of the cases, and that a functionally patent ductus is found in about one-fifth; but the incidence of valve involvement may be

higher, as many cases of this sort are conventionally described simply with reference to the valve abnormality. There is, for example, an excellent photographic reproduction of extensive left ventricular fibroelastosis in Brown's *Congenital Heart Disease* (1950) illustrating a case of aortic atresia. Bower, Gerrard, d'Abreu, and Parsons (1953) gave an account of two cases of congenital mitral stenosis treated by valvotomy, in one of which the ductus was found to be widely patent. They made the distinction between pure congenital mitral stenosis, which may be amenable to operation, and a commoner type associated with other anomalies and regarded as being the mechanical result of unequal division of the primitive atrio-ventricular canal. Fibroelastosis is found in both types. Emery and Illingworth (1951) have also described cases of mitral disease in infancy, noting specially the absence of typical murmurs. The association of endocardial thickening with other congenital anomalies was noted by Henderson, MacGregor, Thannhauser, and Holden (1952), who found it in six of a series of cases of gargoylism, and by Crome (1954), who was able to demonstrate similar changes in the hearts of some cases of epiloia.

The congenital heart abnormality has generally tended to be regarded anatomically, as a mechanical aberration of development, so that references to histology and pathology are very scanty in the older literature of congenital heart disease. Nevertheless Abbott (1908), and numerous previous writers as far back as Laennec and Rokitansky, thought that some of the stenotic forms of congenital heart disease might be due to foetal endocarditis. Since the work of Gross (1941) and others the concept of foetal endocarditis has been replaced by that of endocardial fibroelastosis, considered to be a non-inflammatory process in which there is a pronounced increase in subendocardial fibrous and elastic tissue producing thickening of the mural endocardium and distortion, often to a gross degree, of the affected valves. The manner in which subendocardial fibroelastic thickening leads to ventricular hypertrophy and to the more gradually occurring manifestations of cardiac failure is not known, and has been the subject of much speculation. Degenerative myocardial changes have been described (they are not shown in our cases), and it has been suggested that these changes might result from occlusion of luminal vessels by the fibroelastic layer. Another possibility is that both hypertrophy and failure may be due to the mechanical effect of subendocardial thickening of the heart wall. The typical histological appearances have been described by several of the authors mentioned above, and also in case reports by Vulliamy (1947), Glynn and Reinhold (1950), and others in this country, and are well known.

How, and at what stage of development, the fibroelastic change occurs is also uncertain, but we know that elastic tissue does not normally appear in the heart until the latter half of intrauterine life, and it therefore seems probable that fibroelastosis is also a late change. The course of the illness, particularly in the first of our three cases with gradually developing physical signs, suggests indeed that changes may continue after birth, but we have no clear evidence on this point. A further problem is the exact association of the valvular and

mural changes. The valves are a specialized part of the endocardium, and could therefore be expected to undergo changes similar to those seen in the mural endocardium in response to the same stimulus. Fibroelastosis of the valves was not present in any of our cases; it has, however, been reported by other authors. It is tempting to infer from the occurrence of these two types of case that, in those not showing valvular fibroelastosis, the mural endocardial changes are secondary to primary and much earlier disturbances of valve and septum development, while those showing similar changes in valves and mural endocardium may be the result of some primary disturbance elsewhere. This distinction, if indeed it is a valid one, may not be exclusive, and one might expect to find cases in which both early and late changes have contributed to the final valvular distortion.

There is some evidence that anoxia of the endocardium may be responsible for at least some of the changes seen in these cases. Johnson (1952), in a study of 210 congenitally malformed hearts, found 23 which showed diffuse endocardial fibroelastosis. A careful analysis of these apparently diverse cases revealed that they had in common one feature, namely, the probable occurrence of anoxia of the endocardium, brought about by premature closure of the foramen ovale, by origin of one or both the coronary arteries from the pulmonary artery, or by valvular atresias. A further possibility, not considered by Johnson, is that the endocardial change might occur in response to a slowing of the blood current—a stagnation anoxia; it might also occur as a result of severe anaemia in the mother during pregnancy. One case in which the latter factor may have operated was reported by Menzies and Scott (1954). In this case the mother had a severe anaemia, with haemoglobin in the region of 30 per cent. The infant was in cardiac failure at birth, and lived only for a few minutes. There was extensive fibroelastosis. Cases have, on the other hand, been reported in which considerable cardiac anoxia has not led to any such changes. In one of these, a recent case reported by Tedeschi and Helpern (1954), both coronary arteries were found to arise from the pulmonary artery. No other abnormalities were found either in the valves or in the endocardium. The infant died aged 13 days.

In the three cases reported here definite evidence of foetal anoxia was not obtainable. The coronary vessels in all three were anatomically normal, and only in Case 2 was there a significant degree of valvular stenosis. In all three children the foramen ovale was completely closed. As their ages ranged from six to eight months, premature closure can only be regarded as an unproved possibility. Nevertheless it seems to us, considering these cases and those previously reported, that the views put forward by Johnson to explain the endocardial changes are so far the most acceptable. If they are correct it should be possible to obtain other evidence that anoxia and stagnation in the cardiovascular system may lead to fibroelastosis. Several physiological and pathological observations seem to support this view. Thus the functional closure of the ductus arteriosus at birth must lead to a degree of stagnation anoxia of the intima of this vessel, and in fact within a few weeks anatomical

closure is brought about by a fibroelastic thickening remarkably similar to that which occurs in the hearts we have discussed. The changes leading to obliteration of the hypogastric vessels are of a similar nature. Fibrous and elastic proliferation in the intima is also seen in the mammary arteries after lactation, and in the uterine vessels after pregnancy. This sensitivity of the cardiovascular system to stagnation by reduced blood-flow and anoxia is apparently the method by which the anatomy of the system is adapted to the function it is called upon to serve. Such competence to respond to changes in flow and oxygen supply seems indispensable for the normal development of the heart, since it must maintain its function as a pump throughout its complex embryological and foetal development. As elsewhere in the body, competence of this kind seems to be at a maximum during embryonic life, and stimuli which are adequate then may be quite inadequate in later life to call forth a similar response; hence the rarity of fibroelastosis in adults. The condition of endomyocardial fibrosis seen particularly in Africa belongs to a different category, is due probably to a combination of infection and malnutrition, and is distinguished anatomically by the virtual absence of elastic tissue in the thickened intima (Davies, 1954; Ball, Williams, and Davies, 1954). In the peripheral vascular system, however, where function and demand are constantly changing, the ability to respond in this way is apparently to some extent retained. That it is not entirely lost in the heart, even in old age, is shown by the typical fibroelastosis that may occur in the endocardium over areas of infarction.

Endocardial fibroelastosis is, we suggest, a relatively late developmental abnormality due to the response of the normal endocardium, both mural and valvular, to anoxia, circulatory stasis, or both. On this hypothesis it is the response of a normal tissue to an abnormal stimulus. In the majority of cases the abnormal stimulus arises from previous anomalies of development, such as premature closure of the foramen ovale or valvular abnormalities. In a minority of cases, and where no anatomical cause can be found, it may perhaps be due to an external factor such as a severe anaemia in the mother.

Prognosis and Treatment

Cardiac failure in infancy, when due to structural heart disease, is usually fatal. In a great majority of the cases described the diagnosis has only been made at autopsy. Some reports have appeared, however, of children suffering from the condition here described who have survived beyond infancy. Adams and Katz (1952), in their account of 21 cases, described four children who had survived to the ages of seven months, eight months, 17 months, and three and a half years. One of us (Kempton, 1953) has described a child aged five years who had survived numerous episodes of failure and appeared to be steadily improving, and in whom a diagnosis of endocardial fibroelastosis in the left ventricle seemed justifiable. In this case digitalis was given over a period of three years, and seemed to be of great value in early episodes of failure. The

immediate effect of digitalis was very striking in Case 1 of the present small series, and its value has been noted by several American authors. Infants are known usually to tolerate digitalis in relatively high dosage and, though tolerance varies widely, it seems that up to 0·25 mg. digoxin daily can be given to babies of six months or less, with a careful watch for clinical or electrocardiographic evidence of overdosage. Initial digitalization with a higher dosage may be necessary in severe failure. Nadas, Rudolph, and Reinhold (1953), discussing digitalis therapy in infancy, noted that small infants may need three times the average adult dose of 0·01 mg. of digitoxin per pound of body-weight, and in a number of infants treated since the preparation of this paper began we have used a higher dosage than this with apparently good effect. There is little evidence available as to the value or dangers of mercurial diuretics in infancy. Mersalyl was not tried in our three cases. A further therapeutic possibility is salt-free milk powder, which has recently become available.

It seems that, though the prognosis is so poor, cardiac failure should be treated vigorously in these babies, some of whom may survive for prolonged periods if early failure is recognized and overcome, and some perhaps make a complete clinical recovery. These exceptions may occur particularly in cases in which the abnormality is limited to the mural endocardium. An increasing number of cases, particularly those associated with coarctation of the aorta or patency of the ductus arteriosus, may become amenable to surgery. It is also possible that, as in other diseases, wider recognition of the early clinical features may lead to the discovery of many more and milder cases. It is perhaps significant that in the Registrar General's statistics (1953), next to immaturity, the commonest cause of death in the first year is recorded as pneumonia, accounting for 4·48 deaths per 1,000 live births in 1952. Some, perhaps many, of these deaths may be cases of cardiac failure of the type here described.

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Summary

1. Three cases of endocardial fibroelastosis with associated valve abnormalities are described and discussed, and some previous reports reviewed.

2. Such cases are likely to present in infancy with the more gradually developing manifestations of cardiac failure, often without other evidence of heart disease.

3. Differentiation from technical feeding difficulty and respiratory infection may be very difficult, and cardiac failure in infancy may be much commoner than is supposed.

4. Wider recognition of the early symptoms and signs may lead to more effective treatment, and also to the discovery of milder cases of this type, with a less unfavourable prognosis than is the rule at present.

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FIG. 3. Case 1. Photograph to show opaque thickening of the endocardium of the left ventricle

FIG. 4. Case 1. Photograph showing the thickened endocardium in the left auricle and gross thickening and distortion of the mitral valve

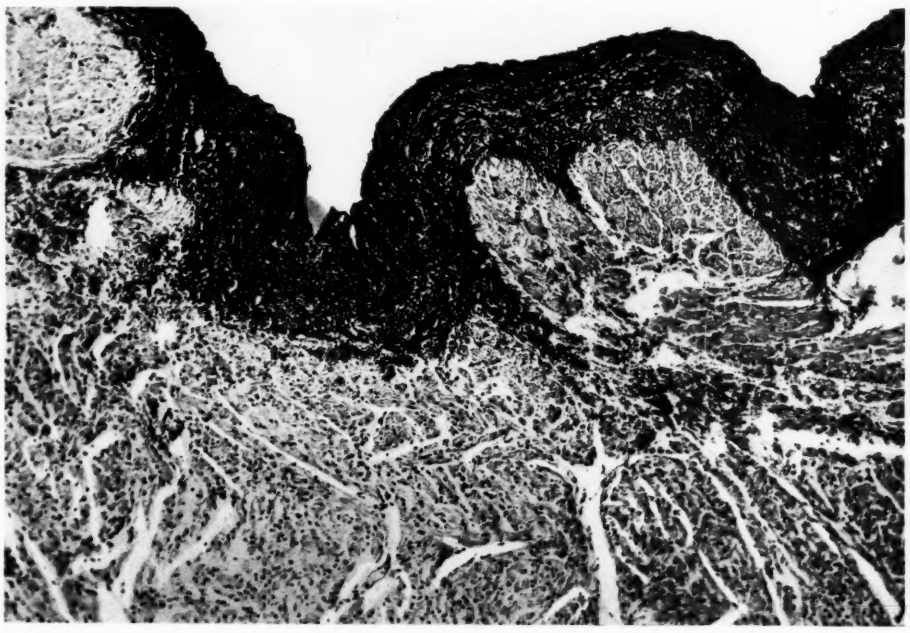

FIG. 5. Case 1. Section of the wall of the left ventricle stained to show elastic fibres (Weigert's stain, × 80)

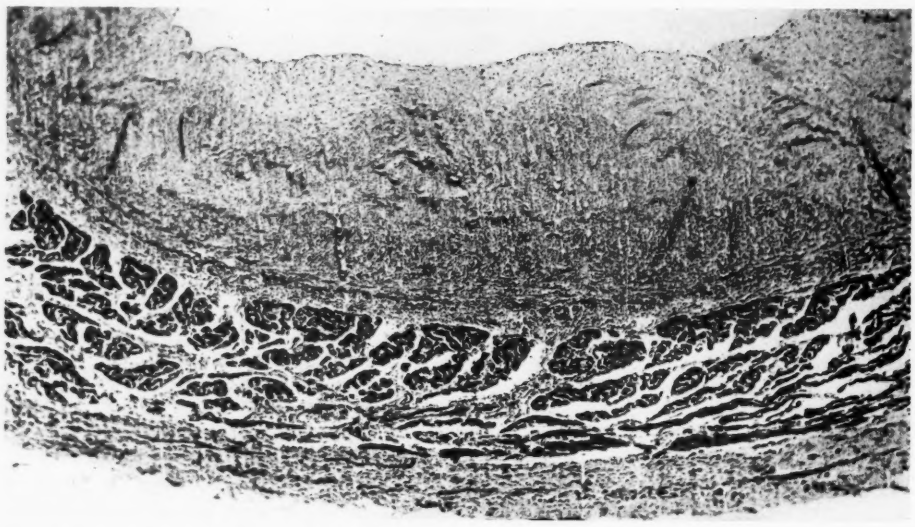

FIG. 6. Case 1. Section of the wall of the left auricle. The subendocardial fibroelastic layer is more than twice the width of the myocardial layer (haematoxylin and eosin, × 30)

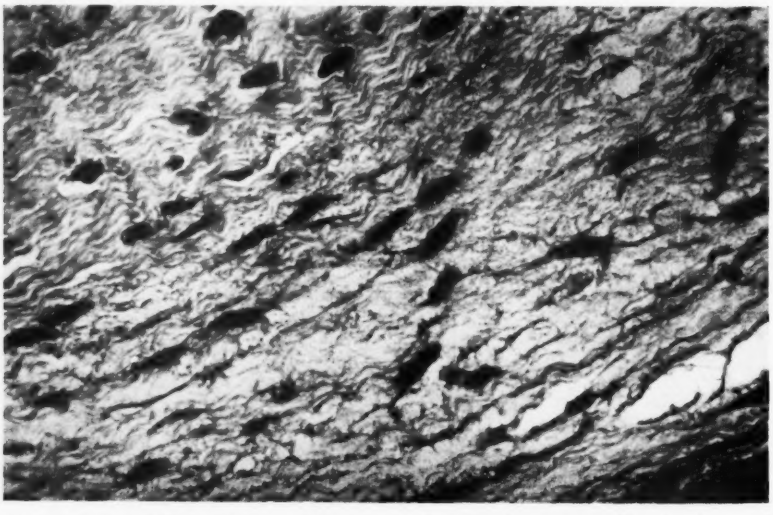

FIG. 7. Case 1. Thickened area of the mitral valve, showing myxoma-like structure and complete absence of inflammatory infiltration (thionin, × 490)

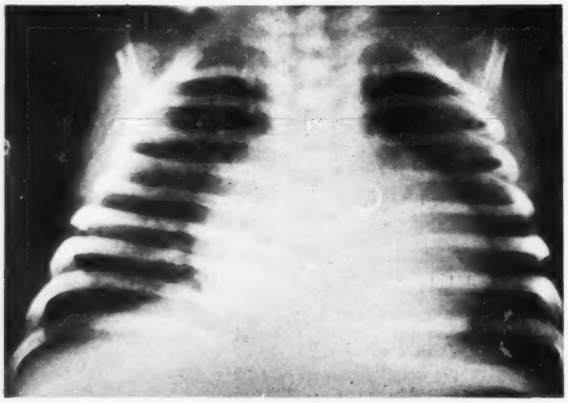

FIG. 8. Case 1. Film showing the globular shape and probable enlargement of the heart shadow

FIG. 9. Case 2. Mitral valve, showing complete fusion of the cusps, and gross thickening and distortion

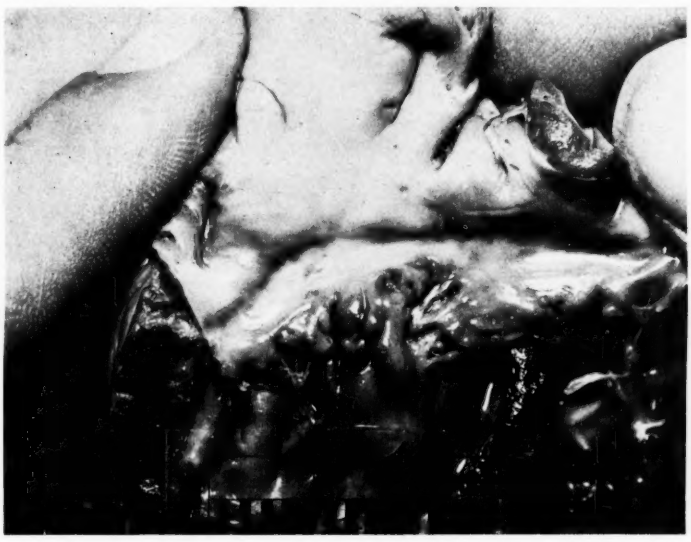

FIG. 10. Case 2. Tricuspid valve, showing remarkable deformity of the cusps, with extreme shortening of the chordae

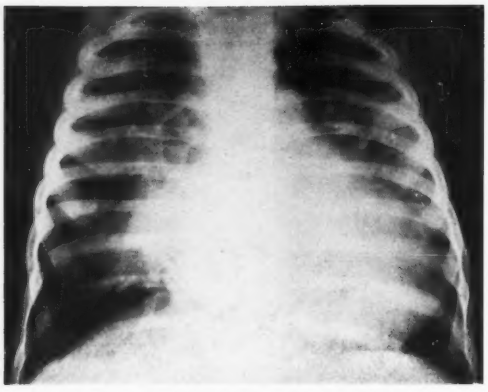

FIG. 11. Case 2. Film showing probable enlargement of the heart, a wide upper mediastinal shadow, and congested lung fields and collapse of the right middle lobe

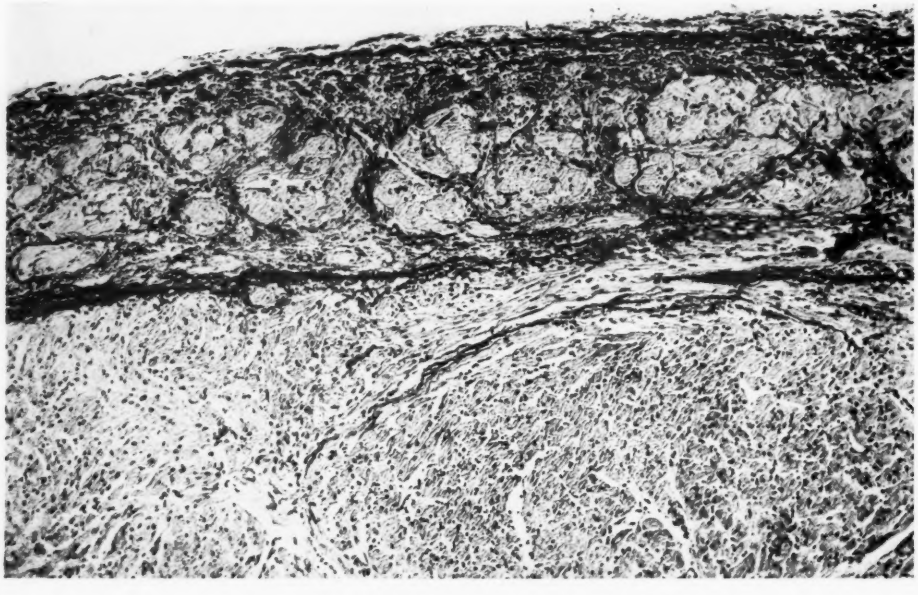

FIG. 12. Case 2. Septal wall of the left ventricle, showing fibrous thickening with incorporation of muscle-fibres (haematoxylin and van Gieson's stain, × 80)

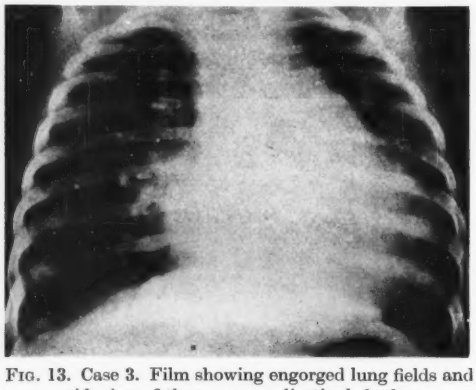

FIG. 13. Case 3. Film showing engorged lung fields and widening of the upper mediastinal shadow

FIG. 14. Case 3. Photograph showing opaque thickening of the endocardium of the left ventricle and fused aortic valves

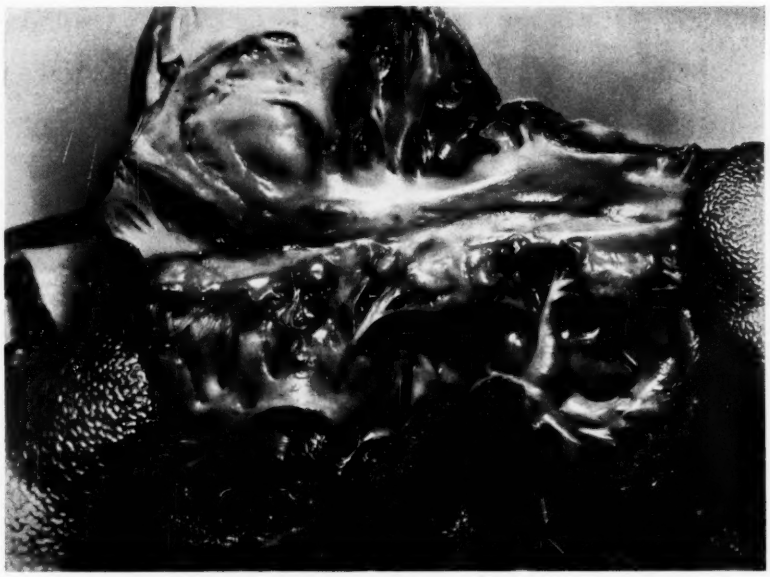

FIG. 15. Case 3. Photograph showing thickening and distortion of the tricuspid valve

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LYMPHOMA OF THE STOMACH AND INTESTINE[1]

By J. F. P. SKRIMSHIRE

(From St. Thomas's Hospital, London)

With Plates 19 and 20

LYMPHOMATA arising in the gastrointestinal tract have excited little comment in England in recent years. In America the condition is well recognized, and has been the subject of numerous reviews and case reports in the past 15 years. Although the growths are uncommon, they are more frequently encountered than is generally recognized. In a five-year period from 1948 to 1953, 18 cases have been seen in the wards of a large teaching hospital, this group of cases forming 10 per cent. of all lymphomata diagnosed at the hospital during that period. The initial symptoms and signs and the natural history of the disease show important differences from those of lymphomata arising elsewhere, and the long survival of a proportion of patients after treatment is striking.

Historical Review

The earliest report of lymphoma in the digestive tract (Briquet, 1838; illustrated in Cruveilhier's atlas, 1842) described enormous enlargement of the gastric rugae due to lymphoid overgrowth, multiple granulomatous tumours throughout the intestine, and generalized glandular enlargement. Cohnheim (1865) described a similar case under the name pseudo-leukaemia, and further reports of widespread involvement of the gastrointestinal tract have appeared from time to time under the names 'lymphogranuloma' and 'pseudo-leukaemia intestinalis'. It is well recognized that the gut may show infiltrations, nodular growths, and diffuse enlargement of the Peyer's patches in patients who die of generalized lymphomata (Boyd, 1944; Jackson and Parker, 1947). Pitt (1889), writing on lymphadenoma of the gut, was the first to review a number of cases in which the disease had evidently arisen in the intestinal tract. He described two forms of growth, one polypoid and the other a tubular infiltration of the bowel sometimes associated with dilatation of the lumen. Fenwick (1901) remarked upon the tendency of these growths to perforate, and Libman (1900) and Jopson and White (1901) recognized the appearance of aneurysmal dilatation of the bowel to be characteristic. Corner and Fairbank (1904), in an extensive review, found the growths to be commonest in the stomach and lower ileum, and described the course of the disease as rapidly fatal with wasting, bowel disturbance, and anaemia. Haggard (1920) reported the first large series of cases of sarcoma of the stomach treated surgically, and more recent accounts have been made by

[1] Received December 8, 1954.

Taylor (1939), Marshall and Meissner (1950), and Snoddy (1952). Intestinal cases have been reviewed by Ullman and Abeshouse (1932), Cameron (1938), and Frank, Miller, and Bell (1942). Numerous case reports have appeared in the last 10 years, the largest personal experience being reported by Usher and Dixon (1943) and Faulkner and Dockerty (1952) from the Mayo Clinic.

The Present Study

The cases described comprise 18 patients seen at St. Thomas's Hospital between October 1948 and September 1953, four cases from the hospital records,

TABLE I

Details of 10 Cases of Lymphoma of the Stomach

Case number	*Age (years)*	*Sex*	*Initial symptoms*	*Appearance of growth*		*Treatment*	*Outcome*
				Macroscopic	*Histological*		
1	56	M	Intermittent indigestion, 3 years	Ulcer, 2 cm. diameter	Reticulum-cell sarcoma	Resection	A. 4½ years
2	40	M	Indigestion 7 years; worse 6 months	Large ulcer, 12×7 cm.	,,	Resection	A. 3½ years
3	50	M	Indigestion, 9 months	Large ulcerated growth	,,	Resection	A.* 5½ years
4	41	F	Epigastric pain and loss of weight, 3 months	Large ulcer, 5 cm. diameter	,,	Resection. Deep X-ray	D. 5 months
5	64	F	Epigastric pain, 3 months	Multiple ulcerated tumours	,,	Resection	A. 4½ years
6	70	M	Known gastric ulcer. Anorexia, 3 months	Multiple ulcerated tumours	,,	Resection	D. 3 months
7	60	M	Perforation. Subsequent indigestion	Large ulcer; 10·5×8·5 cm.	,,	Resection. Deep X-ray	D. 17 months
8	55	M	Perforation. Subsequent indigestion	Large ulcer encircling stomach	Lymphosarcoma	Biopsy. Deep X-ray	D. 2 months
9	74	F	Indigestion, 1 year	Large ulcer, 8×6 cm.	Reticulum-cell sarcoma	Resection	A. 1 year
10	17	M	General malaise	Thickening of pyloric wall. Large rugae	Lymphosarcoma	..	D. 2½ months

A. = alive. A.* = alive, with disease. D. = dead.

and two patients seen at other hospitals. The histological classification of Willis (1948) has been adopted, the following types of tumour being recognized: (1) follicular lymphoma, (2) lymphosarcoma with and without leukaemia, (3) Hodgkin's disease, and (4) reticulum-cell sarcoma.

Age and sex incidence. During the five years 1948 to 1953 lymphomata formed 3 per cent. of all primary malignant tumours of the stomach seen at St. Thomas's Hospital, and 50 per cent. of those in the small intestine. Men were affected more than twice as often as women, and while gastric lymphomata generally occurred after 40 years of age, those in the intestine occured also in younger patients, three of our patients being children. Details of the cases are presented in Tables I and II.

Initial findings. The patients with gastric lymphomata presented one of four clinical syndromes: 1. *Suggesting peptic ulceration.* Recurrent episodes of indigestion, relieved by dieting and alkaline medicines, were present in three patients. 2. *Suggesting gastric carcinoma.* Short histories of pain less clearly related to meals, often severe at night, and associated with anorexia and loss of weight, were described by three patients. A fourth patient, known to have a chronic gastric ulcer, developed increasingly severe symptoms, and was

TABLE II

Details of 14 Cases of Lymphoma of the Intestine

Case number	*Age (years)*	*Sex*	*Site of growth*	*Initial symptoms*	*Appearance of growth*		*Treatment*	*Outcome*
					Macroscopic	*Histological*		
11	76	M	Ileum	Acute obstruction	Three plaques, two perforated, in ileum	Reticulum-cell sarcoma	Resection	D. 4th day
12	54	M	Ileum	Subacute obstruction, 1 week	Extensive multiple infiltrations. Mucosa intact	,,	Biopsy	D. 2nd day
13	20	F	Ileum	Recurrent obstruction, 6 months	Single polypoid tumour; intussusception	,,	Resection	A. 3½ years
14	12	F	Ileum	Recurrent obstruction, 1 month	Ulcerated growth leading to stenosis	,,	Resection	A. 3 years
15	56	M	Duodenum	Pyloric obstruction, 3 months	Ulcerated tumour with obstruction	Lymphosarcoma	Biopsy	D. 3 months
16	14	M	Ileum and caecum	Recurrent obstruction, 3 weeks	Multiple polypoid tumours; intussusception	,,	Resection. Deep X-ray	D. 6 weeks
17	68	M	Ileum	Perforation	Infiltration with perforation	Reticulum-cell sarcoma	(1) Suture and biopsy. Deep X-ray (2) Exploration	D. 10 months
18	64	M	Ileum	Perforation on two occasions	Aneurysmal dilation with perforation	,,	Resection. Deep X-ray	D. 11 months
19	42	F	Jejunum	Diarrhoea, 4 months	Extensive infiltration	Follicular lymphoma	Biopsy. Deep X-ray	A.* 6 years
20	8	M	Ileum	Diarrhoea, 6 months	Chronic intussusception; polypoid tumour	Lymphosarcoma	,,	D. 3 weeks
21	54	M	Duodenum	Indigestion 1 year. Haematemesis	Ulcerated tumour	Reticulum-cell sarcoma	Biopsy. Deep X-ray	D. 10 months
22	38	M	Ileum	'Appendicitis'	Two infiltrations in terminal ileum	Lymphosarcoma	Biopsy	D. 2nd day
23	52	F	Ileum	Abdominal pain, 10 days	Ulcerated tumour. No obstruction	Reticulum-cell sarcoma	Resection	D. 1 year 11 months
24	40	M	Widespread	Ascites, 8 days	Diffuse peritoneal growth	,,	Biopsy. Radioactive colloidal gold	D. 6 months

A. = alive. A.* = alive, with disease. D. = dead.

thought to have malignant change in a pre-existing benign peptic ulcer. 3. *With perforation.* Two patients, without previous histories of indigestion, had signs of perforation. Both were treated surgically, and the perforations were considered to be due to peptic ulceration. 4. *Without local symptoms.* One patient, details of whose illness were obtained from the hospital records, complained of general malaise and of loss of weight, but no symptoms referable to the digestive tract. Autopsy shortly afterwards showed widespread lymphosarcomatous growth, but the most striking findings were in the stomach, where it seemed probable that the growth had originated.

It will be seen that indigestion was the commonest symptom in these patients. Diminished appetite and loss of weight were also noticed by seven patients, and vomiting occurred in three, but was neither copious nor blood-stained.

The patients with growths in the intestine described symptoms of short duration and sometimes with an acute and severe onset. Four were admitted to hospital within 12 hours of the onset of their illness, and in only one case had symptoms been present for more than six months. Three groups of symptoms were observed, the first being much commoner than the others; a fourth group comprises a variety of symptoms. 1. *Symptoms of obstruction.* Central abdominal colic and vomiting suggested obstruction of the small bowel in six patients. In one case obstruction was acute and associated with perforation, in two it was subacute, and in three there were recurrent episodes at intervals of a few days or weeks. 2. *Perforation.* Two patients presented signs of perforation, one of them experiencing a second episode eight months later. At operation the perforations were found to be in the ileum in both cases. 3. *Diarrhoea.* Chronic diarrhoea was the complaint of two patients. In one (Case 19) the frequency and character of the stools suggested steatorrhoea, but fat balances demonstrated normal absorption. In the other (Case 20) there was a chronic intussusception, which was not recognized during life. 4. *Miscellaneous symptoms.* Severe haematemesis and melaena, abdominal pain suggesting acute appendicitis, and ascites each occurred in one instance.

Examination. Loss of weight of variable extent had been noticed by more than half the patients, but severe wasting and cachexia were not seen. Abdominal tumours were felt in 14 patients (56 per cent.); they were generally large, mobile, and slightly tender. In most cases they represented the primary growth and associated lymphatic glands, but in three patients they were later shown to be intussusceptions. Fever was rare, anaemia was not prominent, and evidence of growth elsewhere in lymphatic glands, spleen, or liver was unusual. In one patient enlarged inguinal glands suggested the presence of a malignant tumour, and in another patient the spleen became palpable six months after the onset of symptoms, but before a diagnosis had been established.

Investigations. Radiology was the most useful and important diagnostic investigation. Gastric analysis showed histamine-fast achlorhydria in half the patients who had gastric lymphomata, and occult blood was found in the stools of the three patients with intestinal tumours who were examined in this way. Gastroscopy was not employed in any of our cases. Barium meals demonstrated

neoplasms in the majority of patients who had tumours in the stomach or duodenum, but no special features were recognized to distinguish lymphoma from carcinoma. In one patient a barium enema showed an intussusception with a tumour at its apex, but in the majority of those who had intestinal tumours the indications for surgical exploration were so strong that routine radiological examinations were not carried out. In the only patient (Case 19) in whom small-bowel radiography was undertaken two separate examinations failed to show any abnormality, although a large segment of jejunum was infiltrated with growth.

Treatment and findings at operation. Twenty-two patients were operated upon, eight gastric and six intestinal tumours being removed, and biopsies taken from the remainder. The local lymphatic glands were enlarged in every case, but histological examination did not always confirm the presence of growth. In five patients the finding of plaques of growth in the bowel wall, perforations, or both together, was very suggestive of lymphoma. This diagnosis had not been previously considered in these cases, and the significance of the appearances was not always appreciated at the time of operation. In one patient (Case 8), who had a perforation of the stomach, the surgeon noticed that the edges of the perforation were indurated and that closure was more difficult than usual, and in another (Case 17) similar appearances around a perforation of the ileum led to a biopsy, from which a diagnosis of reticulum-cell sarcoma was established. Deep X-ray therapy was given to 10 patients, only one of whom had had a satisfactory removal of the primary growth. Radioactive colloidal gold was used in the patient who had ascites.

Pathology. 1. *Macroscopic appearances.* The growths were of three varieties, illustrated in Plates 19 and 20 (see also Tables I and II). (1) *Single ulcers.* Seven of the growths in the stomach were of this type, five of them exceeding 5 cm. in diameter (Plate 19, Fig. 2). Both duodenal growths were ulcerative, and one in the ileum was associated with stenosis of the lumen of the bowel (Plate 20, Fig. 4). (2) *Single or multiple polypoid growths.* Two patients with gastric lymphomata had multiple tumours arising sharply from the normal mucous membrane to a height of 1 to 2 cm. The tops of these tumours had become ulcerated, so that the tumours were largely excavated (Plate 19, Fig. 1). Three patients had such growths in the intestine, and in each case intussusception had occurred. (3) *Diffuse infiltration or multiple plaques.* This was the commonest variety of growth in the intestine, but only one example was observed in the stomach. Three were associated with perforation, and in one there was also aneurysmal dilatation of the bowel (Case 18; Plate 20, Fig. 5). In one patient (Case 10) the pyloric end of the stomach was diffusely infiltrated and thickened with growth; the rugae were greatly enlarged, and scattered among them were numerous nodules of growth. The specimen is not now available for examination, but Plate 20, Fig. 3, from a specimen in St. Thomas's Hospital Museum, shows the appearances very well.

2. *Histology.* The tumours were classified as follicular lymphoma in one case, reticulum-cell sarcoma in 17 cases, and lymphosarcoma in six cases.

Considerable variation in detailed histology was observed in three of the tumours and affected lymphatic glands, and made accurate classification difficult. For example, the tumour removed from the stomach in Case 3 showed the appearances of reticulum-cell sarcoma, while sections from glands removed at a later date showed the picture of Hodgkin's disease.

Course. Five of the patients who had growths in the stomach are alive and well from one to five and a half years after removal of their tumours. One of them (Case 3) has had glands containing growth removed from the neck since his original operation, but although radiotherapy has not been given he remains free from symptoms, and there is no clinical evidence of growth four and a half years after the last gland was removed. Of the five fatal cases, four patients died within six months of admission to hospital, and the fifth survived 17 months after partial gastrectomy and radiotherapy. In every case but one there had been severe local recurrence and spread of growth.

The patients who had intestinal growths have shown a poorer prognosis, only three of 14 remaining alive at the present time. One of these three is deteriorating, with widespread disease, six years after the discovery of inoperable follicular lymphoma of the jejunum. The other two patients are well three and a half and three years after removal of growths from the ileum. Three patients died in the period immediately following operation, four within six months of admission, and three more within a year. One patient survived almost two years after removal of a tumour from the ileum.

Post-mortem examinations have shown widespread disease in a few patients, all of whom were young (Cases 10, 16, and 20). In Case 20 all the lymphatic glands in the neck, mediastinum, and abdomen were slightly enlarged and contained growth. There were deposits in the lungs and pleurae, with bilateral pleural effusions. A large intussusception was present in the transverse colon, its apex being formed by the ileocaecal segment, which contained a necrotic polypoid growth. The mesentery in relation to this portion of the gut was infiltrated, and a few small plaques of growth were present on the surface of the gut elsewhere. The spleen was normal in size, but the liver and both kidneys contained numerous deposits of growth. More commonly there has been a remarkable local spread of growth in the peritoneal cavity, with inconspicuous deposits elsewhere. One patient (Case 8) had an inoperable growth in the stomach treated with radiotherapy. Autopsy showed extensive infiltration of the distal half of the stomach, with direct spread into the liver and pancreas. The posterior abdominal wall was invested with a sheet-like layer of growth which spread upwards over the anterior aspect of the kidneys, under the diaphragm, and over the surface of the spleen. The glands round the coeliac axis were enlarged and contained growth, but those in the mediastinum and neck were normal. Apart from the direct spread described, the liver was free from growth and no more distant deposits were found. Very similar appearances were present at post-mortem examination in another patient (Case 7), who survived 17 months after removal of a reticulum-cell sarcoma of the stomach and subsequent radiotherapy.

With one notable exception, all the surviving patients have had their growths removed, but radiotherapy has not subsequently been given. In this one instance (Case 19) successive courses of deep X-ray treatment on three occasions have been followed by marked clinical improvement. She began to have diarrhoea when 42 years old, in October 1948. When seen six months later she had lost weight, and had developed oedema of the ankles owing to hypoproteinaemia. Laparotomy in October 1949 showed a large segment of jejunum thickened and infiltrated with growth, and enlarged abdominal glands. Microscopic examination of a portion of excised gut showed follicular lymphoma. Radiotherapy led to relief of diarrhoea, gain in weight, and reversion of the plasma-proteins to normal. Further courses of treatment were given in May 1952 for recurrent abdominal pain and diarrhoea, and in October 1953 because of subacute intestinal obstruction. During the past year groups of enlarged glands in the neck and axillae have also been irradiated, but her general condition is now only fair, and it is clear that the growth is becoming widely generalized.

Discussion

The age incidence and sex incidence of the patients in the present series do not differ in any important respect from those given in previous accounts. The growths were commonest in the stomach and ileum, but only one was seen involving the large bowel, where one-third of the growths are reported to arise (Ullman and Abeshouse, 1932; Taylor, 1939; Usher and Dixon, 1943).

Symptoms. In the majority of patients the symptoms had no special characteristics, growths in the stomach suggesting peptic ulceration or carcinoma, and those in the intestine commonly producing obstruction. An important group of patients, however, had acute symptoms with a severe onset due to perforation, haemorrhage, or obstruction. Perforation has long been recognized as occurring in this type of growth (Fenwick, 1901), but recent accounts include very few examples (Bradmore and Scorer, 1953). Five patients of the present series were seen on account of perforations (20 per cent.), and one of them had a second episode. The frequency of haemorrhage varies considerably in different reports, some authors claiming that it occurs in half the cases (Spellberg and Zivin, 1949; Elliott and Wilson, 1952), but in our experience it is uncommon. Obstruction, which occurs in half the patients with intestinal growths (Cameron, 1938), was generally subacute or recurrent in our patients, but in one instance it was acute and associated with perforation.

Diagnosis. On examination of the patients palpable tumours were found in more than half the cases, but, although some loss of weight was common, we were impressed with the well-nourished appearance of the majority. The absence of signs of growth elsewhere in the body has already been noted. All writers agree that the clinical recognition of lymphomata in the digestive tract is difficult. The principal features which suggest the diagnosis depend upon the tendency of the growths to be multiple and to produce extensive infiltrations. These characteristics may occasionally be demonstrated radiologically, and in

the stomach they may be seen at gastroscopy. Infiltrating growths may produce two highly characteristic appearances, both of which are uncommon. In the stomach they lead to enlargement and rigidity of the mucosal folds, and on gastroscopy polypoid nodules of growth and shallow ulcers may be seen among the abnormal folds. Some thickening of the gastric rugae is common in association with peptic ulceration, carcinoma, and gastritis, and, while expert gastroscopists recognize that the distinction from lymphoma may sometimes be difficult without biopsy, an increasing number of correct diagnoses are being made in this way (Schindler, 1950). In the intestine, particularly the small bowel, infiltrating growths may be associated with aneurysmal dilatation of the lumen. These dilatations may be multiple, and on X-ray examination they appear as smooth saccular or fusiform enlargements, separated by narrower segments of bowel where the mucosal pattern is normal (Doub, 1947). Even when this characteristic appearance is not seen, the extensive nature of the lesion may suggest lymphoma, carcinoma and other tumours in the small bowel usually being sharply localized in their extent (Swenson, 1943). In the present series we have encountered only two growths of this characteristic infiltrating type, giving rise to enlarged gastric rugae in one case and aneurysmal dilatation of the ileum in the other. Our experience and study of the literature suggest that the frequency of this easily recognizable type of growth has been overemphasized in the past. The uncertainty of clinical diagnosis and the importance of histological evidence of the nature of the growth necessitate surgical exploration in most cases. The appearances at operation may indicate a diagnosis of lymphoma when this has not previously been suspected, as happened in five cases in the present series. Infiltration of a segment of bowel or plaques of growth in the bowel wall are very suggestive of lymphoma, and the occurrence of perforation in such abnormal areas is characteristic. Perforation in an unusual site should always suggest the possibility of lymphoma, and biopsies should be taken when possible.

Treatment. There is general agreement that the growths, with their immediate area of lymphatic drainage, should be resected if this is possible. The present study confirms previous reports (Taylor, 1939; Marshall and Meissner, 1950) that a large proportion of the gastric tumours can be removed in spite of their size, and that the operability rate is considerably higher than for carcinoma. In the intestine we have found the tumours less frequently operable because of involvement of the abdominal glands. The lymphomata are sensitive to radiotherapy, and relief of symptoms, improvement in X-ray appearances, and occasionally long survival may follow deep X-ray treatment (McSwain and Beal, 1944; Marcuse and Stout, 1950). Unless particular contra-indications are present, such as the production of an artificial menopause in a young patient, we agree with other writers that radiotherapy should be given after successful surgical removal of a growth.

Pathology. The growths are believed to originate from the submucous lymphoid follicles, and to spread along the tissue planes, often separating the mucosa from the muscularis. Localized proliferation may give rise to polypoid

tumours, and infiltration beneath the mucous membrane gives rise to the characteristic thickening and broadening of the mucosal folds which is seen in some cases. Lymphomata excite little reaction in the tissue of their origin, and this may explain the frequency with which necrosis of a growth leads to perforation, and the rarity of stenotic lesions in the intestine. Ulcerative, polypoid, and infiltrating growths have previously been described by Pack and McNeer (1935) and other writers. We have been impressed with the frequency and size of ulcerative growths in the stomach, and the tendency for infiltrating growths to occur in the intestine and to be associated with perforation. Polypoid growths in the intestine commonly give rise to intussusception, and the three instances in the present series all showed this complication.

The progress of the disease can be satisfactorily explained in many cases by local extension of growth and lymphatic spread. In a few, particularly those in which the growths are multiple, the pattern of the disease can only be explained by a multifocal origin of growth. The long survival of some patients after excision of a primary growth indicates, however, that this is not an invariable feature of the disease. Our experience demonstrates that local spread of growth in the abdominal cavity is the commonest cause of death. Widespread growth of metastatic or multifocal origin is often inconspicuous, and more commonly seen in the younger patients. In children a leukaemic termination of the illness is not uncommon (Cutler, Stark, and Scott, 1945).

The majority of the tumours are described as lymphosarcoma or reticulum-cell sarcoma. Histological details often vary considerably in different parts of the tumours and in the affected lymphatic glands, making assignment to a rigid histological category difficult. Such variations, which were present in three of our cases, are not unexpected, and provide further support for the belief that the tumours, arising in lymphatic tissue, are derived from primitive mesenchymal cells with a potentiality for differentiation in widely different directions (Custer and Bernhard, 1948; Maximow and Bloom, 1948; Willis, 1948). The macroscopic appearances of the growths and their behaviour are not related to the histological findings, and, while follicular lymphoma is recognized to have the best prognosis, no significant difference in survival between patients with lymphosarcoma and those with reticulum-cell sarcoma has been demonstrated (Usher and Dixon, 1943; Marcuse and Stout, 1950).

Course and prognosis. The natural course of the disease is usually short. Symptoms are present for an average period of six to 12 months before the diagnosis is made, and even after treatment half the patients die within a year. In children the disease is more rapidly fatal; Simpson-Smith (1938–9) found that 60 per cent. of those affected died within six months. In a few cases the disease has been observed over a number of years with little or no treatment, and other patients have been described in whom symptoms had been present up to five years before the diagnosis was established (Marcuse and Stout, 1950). Cardon and Greenebaum (1945) observed a case for four years without specific treatment, and Taylor (1939) reported a man who suffered two episodes of perforation of a gastric lymphoma, and survived for more than five years after

simple surgical repair and an incomplete course of radiotherapy. The long survival of one of our patients (Case 3) is similarly unexpected. After treatment between 10 and 15 per cent. of patients survive for more than five years, the majority having had their growths surgically removed. The longest survival, 29 years, is recorded by Usher and Dixon (1943), and suggests that surgery may sometimes result in complete cure.

The site of the growth appears to have an important bearing on prognosis, probably by affecting the ease with which surgical excision can be carried out in different situations. Growths in the duodenum, for example, can rarely be removed, and no long survival has been reported when the growth was in this situation. Growths in the stomach, on the other hand, can be removed in a high proportion of cases; Marshall and Meissner (1950) reported 12 (37·5 per cent.) of 32 patients treated at the Lahey Clinic surviving for more than five years, and Madding and Walters (1940) found an average survival of four to five years in their patients. Usher and Dixon (1943) described a remarkable prognosis for patients with growths in the caecum. Resection of growth was achieved in 17 of 18 cases, and nine of the patients survived more than five years. This result contrasts strikingly with the fate of 33 patients in the same clinic, with tumours in the small intestine, described by Faulkner and Dockerty (1952); in all except one the growths were removed, but only three patients survived for more than five years. A marked difference in behaviour of growths in the caecum and ileum is difficult to explain and, in studying the reports of long survivals, no such difference has been discerned. In our experience tumours in the intestine are less readily removed than those in the stomach, and the prognosis in these patients is correspondingly worse.

It is evident, therefore, that there is great difficulty in evaluating the prognosis in lymphomata of the alimentary tract. A few patients survive for long periods after successful surgical removal of growth, and occasionally after apparently inadequate treatment, while the majority of cases are rapidly fatal in spite of surgery and deep X-ray therapy. The present study confirms the better prognosis for patients with lymphoma of the stomach, but does not provide any new information of value in assessing the prognosis in a particular case. The long survival of a proportion of patients after surgical treatment suggests that the tumours may remain localized, at least for a time, and that their removal may be followed by cure. It is suggested that surgical treatment might with advantage be extended to include the removal of any lymphomatous process which appears confined to a local site or group of lymphatic glands.

Acknowledgements

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Summary

1. An account is given of 24 cases of primary lymphoma of the gut. The tumours are more common than is generally realized and, in the period 1948 to 1953, 10 per cent. of all lymphomata diagnosed at St. Thomas's Hospital arose in the gastrointestinal tract.

2. The symptoms are sudden in onset in a proportion of patients because of perforation, obstruction, or haemorrhage. In the present series 20 per cent. of patients had perforations.

3. Recognition of the growths is difficult on clinical examination or at operation. The most suggestive features are due to the tendency for the growths to be multiple and to produce extensive infiltrations. These characters may be recognized radiologically, gastroscopically, or at operation.

4. Histological recognition of the nature of the growths is important because of their sensitivity to irradiation.

5. The course of the disease is usually short, half the patients dying within a year of the diagnosis being made. Post-mortem examinations frequently show very extensive local spread of growth throughout the peritoneal cavity, and absent or inconspicuous distant foci of growth.

6. Approximately 10 per cent. of all patients, and a greater proportion of those with gastric lymphomata, survive for more than five years. The prognosis is difficult to evaluate, and no further information of value in this respect has emerged from the present study.

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FIG. 1. Multiple excavated reticulum-cell sarcomata of the stomach (Case 6)

FIG. 2. Large ulcerating reticulum-cell sarcoma of the stomach (Case 9)

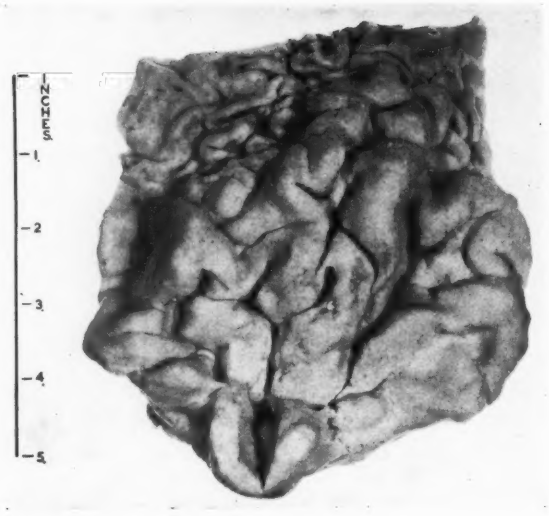

FIG. 3. Enlargement of the rugae of the stomach due to lymphosarcoma (St. Thomas's Hospital Medical School Museum)

FIG. 4. Ulcerating reticulum-cell sarcoma of the ileum with stenosis (Case 14)

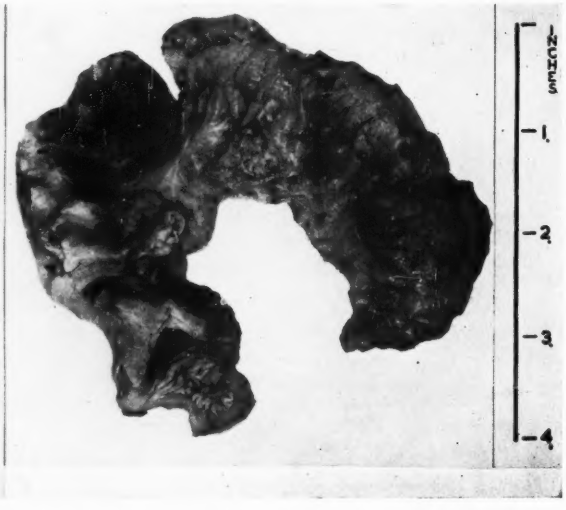

FIG. 5. Infiltrating reticulum-cell sarcoma with aneurysmal dilatation of the ileum and perforation (Case 18)

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CORTICOTROPHIN AND CORTISONE IN THE TREATMENT OF SCLERODERMA[1]

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With Plate 21

Since scleroderma was first mentioned by Zacutus in 1634 (Jadassohn, 1931) many forms of treatment have been used. While there have been occasional reports of benefit, sometimes striking, nothing has yet been shown to cure the condition, or even to produce lasting improvement. Klemperer, Pollack, and Baehr (1942) classed scleroderma among the diffuse collagen diseases. With the advent of corticotrophin and cortisone as effective agents in certain rheumatic and collagen diseases, their use in the treatment of scleroderma seemed rational. Among the early trials there were conflicting reports, some workers obtaining good results (Bayles, Sout, Stillman, and Lever, 1950; Kierland and Hines, 1951; Taubenhaus and Lev, 1951; Frank and Levitt, 1952), while others (Thorn, Forsham, Frawley, Hill, Roche, Staehelin, and Wilson, 1950; Briggs and Illingworth, 1952) recorded no improvement. Thorn and his colleagues stated that there was no evidence at that time that cortisone in any way altered the fundamental course of the disease. The present report deals with the effects of treatment with cortisone and corticotrophin in 14 patients suffering from scleroderma.

Patients Treated and Methods Used

There were seven female and seven male patients, and their ages ranged from 23 to 70 years. In nine patients scleroderma was associated with peripheral vascular disturbances of the Raynaud type; in the remaining five there were no vasospastic phenomena. In one of the former and one of the latter group the sclerodermatous changes were confined to the hands, but in the remainder there was more generalized involvement of the skin. Six patients had evidence of visceral involvement. The duration of the symptoms of scleroderma prior to the onset of treatment with corticotrophin or cortisone varied from three months to 12 years, and seven patients had previously received other forms of therapy. In all the patients the diagnosis of scleroderma was confirmed by histological examination of a biopsy specimen of skin, and the following investigations were made prior to treatment and repeated at intervals during therapy: radiography of the chest, oesophagus, gastrointestinal tract, skeleton, and soft tissues of the limbs; electrocardiography; blood counts and estimations of the erythrocyte sedimentation rate (Wintrobe); serum-protein estimations, and the following

[1] Received February 11, 1955.

tests related to the serum-proteins ('liver function tests'): γ-globulin, thymol turbidity, thymol flocculation, and Takata-Ara tests; and the differential sheep-cell agglutination test (Rose, Ragan, Pearce, and Lipman, 1948). The salient clinical features of each case are summarized in the Table.

Eight patients received both corticotrophin and cortisone for different periods, and six received cortisone alone. Corticotrophin was given by subcutaneous injection of 15 to 25 i.u. every six to 12 hours, or by daily intravenous infusions of 20 mg. during eight-hour periods, or by intramuscular or subcutaneous injection of 40 to 80 mg. of the gel once daily. Cortisone was given orally in doses of 200 to 300 mg. on the first day, 100 to 200 mg. on the second day, 100 mg. on the third day, and thereafter a maintenance dose of 50 to 150 mg. daily. All patients received potassium chloride, 4 to 6 gm. orally daily, and were advised to restrict their intake of salt. The duration of therapy varied from three weeks to two and a half years, and the patients were observed at regular intervals during this period. In four patients (Cases 4, 5, 6, and 10) second histological examinations were performed on specimens of skin obtained from areas immediately adjacent to those originally examined.

Results

The patients have been divided into four groups according to their response to treatment:

Group I. Therapy produced marked beneficial effects: one patient (Case 5). The criteria were (1) complete disappearance of symptoms; (2) complete disappearance of clinical and histological evidence of scleroderma; (3) no relapse during treatment with an effective dosage.

Group II. Therapy produced moderate beneficial effects: three patients (Cases 6, 8, and 13). The criteria were (1) marked alleviation of symptoms; (2) objective improvement, but not complete disappearance of clinical signs; (3) no relapse during treatment with an effective dosage.

Group III. Therapy produced slight beneficial effects: nine patients (Cases 1, 2, 4, 7, 9, 10, 11, 12, and 14). The criteria were (1) improvement in symptoms; (2) little or no objective improvement; (3) possible relapse during treatment with an effective dosage.

Group IV. Therapy produced no beneficial effects: one patient (Case 3). The criteria were (1) no subjective improvement apart from a general feeling of well-being; (2) no objective change.

The duration of treatment and the response in each patient are indicated in the Table.

Illustrative Case Reports

Group I

Case 5. A 69-year-old male clerk was seen in October 1951, and complained of stiff painful hands of five months' duration. The hands had become puffy, and his grip weak. Aspirin (gr. 15 four-hourly) was necessary for relief of the pain. The skin of both hands and over the chest and back was thickened and oedematous, and he was unable to close the fists completely. There was no evidence of

Clinical Data, Duration of Therapy, and Response

Case number	*Sex*	*Age (years)*	*Duration of symptoms before treatment*	*Extent of skin involved*	*Visceral involvement*	*Raynaud's phenomenon*	*Duration of treatment*	*Response to treatment*
1	M	40	7 years	Whole body	Oesophagus	Mild	23 months	Slight improvement; no progression of the disease
2	F	44	5 years	Upper and lower limbs, upper part of chest, face	Oesophagus, heart	Severe	1st course: 5 months	Slight improvement; stopped treatment because of development of painful ulcers on finger-tips
							2nd course: 1 week	No improvement; developed fatal bilateral lobar pneumonia
3	F	27	2 years	Hands, forearms, face, feet	Nil	Severe	3 weeks	No improvement
4	F	28	1 year	Hands, arms, face	Nil	Severe	1st course: 10 days	Slight improvement
							2nd course: 13 months	Slight improvement; no progression of the disease
5	M	70	5 months	Hands, trunk	Nil	Nil	29 months	Marked improvement; no clinical or histological evidence of scleroderma while on treatment; relapse on temporarily stopping treatment
6	M	70	6 months	Hands, forearms, chest, legs	Oesophagus	Nil	21 months	Moderate improvement; no progression of the disease
7	M	45	12 years	Whole body	Oesophagus, heart, lungs	Severe	7 weeks	Slight improvement; stopped treatment of own accord and did not return for follow-up
8	M	60	3 months	Hands	Nil	Nil	1 month	Moderate improvement; stopped treatment of own accord and did not return for follow-up
9	F	47	1 year	Upper and lower limbs, face	Oesophagus	Severe	1st course: 3 weeks	No improvement
							2nd course: 5 months	Initial slight improvement; while on treatment developed hypertension and an epileptiform seizure, and subsequently acute pancreatitis complicated by lower-nephron nephrosis, from which she died
10	M	23	5 months	Hands, forearms, legs	Nil	Moderate	28 months	Slight improvement; no progression of the disease
11	M	45	6 months	Arms, chest	Heart, ? lungs	Nil	11 months	Slight improvement; no progression of the disease
12	F	48	4 years	Hands	Nil	Moderate	14 months	Slight improvement; no progression of the disease
13	F	44	6 months	Hands, forearms, legs	Nil	Nil	30 months	Moderate improvement; no progression of the disease
14	F	38	6 months	Upper and lower limbs, face	Nil	Severe	6 months	Slight improvement; no progression of the disease

a vasospastic disturbance. The blood-pressure was 130/80 mm. Hg, and examination of the other systems was negative. A blood count revealed a moderate polymorphonuclear leucocytosis, but a second count was normal. The erythrocyte sedimentation rate was 26 mm. in one hour. The total serum-proteins were 6·7 gm. per 100 ml. (albumin 3·5 gm., globulin 3·2 gm.); thymol turbidity 3 units; Takata-Ara reaction+; thymol flocculation+. Rose's differential sheep-cell agglutination test was negative. An electrocardiogram showed inversion of the T wave in leads V_4, V_5, and V_6. Radiological examination of the heart, lungs, alimentary tract, skeleton, and soft tissues of the limbs showed no abnormalities. Skin biopsy from a finger revealed the typical histological picture of scleroderma, with hypertrophic epithelium, hyperkeratosis, flattening of the rete pegs (epidermal ridges), and increased bulk and density of the collagen fibres (Plate 21, Fig. 1).

Corticotrophin therapy was begun with a total daily dosage of 60 i.u., given in four doses by intramuscular injection. After two days pain was relieved, and two days later the stiffness and swelling disappeared and the patient was able to make a complete, tight fist. On the 15th day of treatment corticotrophin was reduced to a total of 45 i.u. daily given in three doses. He was discharged from hospital free from symptoms, to continue maintenance therapy at his home with 30 i.u. of corticotrophin daily, divided into two doses. Investigations at this time gave the following results: erythrocyte sedimentation rate, 1 mm. in one hour; total serum-proteins 6·0 gm. per 100 ml. (albumin 3·5 gm., globulin 2·5 gm.); thymol turbidity 1·0 unit; thymol flocculation test negative; Takata-Ara test negative. The electrocardiogram was unchanged.

Six weeks later (December 29, 1951) he was readmitted complaining of a recurrence of pain and stiffness in the fingers. In the interval he had frequently omitted the injections for a few days at a time. Examination revealed thickening and oedema of the skin over the dorsum of the hands and over the trunk. Corticotrophin was continued in the dosage of 30 i.u. daily until January 10, 1952, when cortisone was substituted in a dose of 75 mg. daily. Two days later he was relieved of all symptoms, and after a further five days the swelling and thickening had disappeared and the skin presented a normal appearance. On the 20th day of cortisone therapy a second specimen of skin, taken from an area immediately adjacent to that of the first, revealed a normal histological picture. The epithelial hypertrophy had disappeared, and there was less hyperkeratosis. The rete pegs were normal, and the collagen tissue had loosened and was less compact (Plate 21, Fig. 2). The electrocardiogram still showed inverted T waves in leads V_4, V_5, and V_6.

During 1952 cortisone was continued in a daily dosage varying from 50 to 75 mg., and the improvement was maintained. In February 1953 therapy was gradually discontinued; the patient remained well for the next 10 days, then pain and stiffness, with swelling of the dorsum of both hands, rapidly returned. One month later the pain was so severe, and the impairment of the patient's working ability so great, that he requested that cortisone therapy be reinstituted. Cortisone was given in an initial dosage of 300 mg., 200 mg., and 100 mg. on consecutive days, followed by a daily maintenance dose of 75 mg. Dramatic regression of symptoms again occurred. Therapy has been continued up to the time of writing, that is for 29 months, and the patient remains free of symptoms. Objectively no evidence of scleroderma is apparent, and yet with each attempt at discontinuing cortisone the clinical manifestations of the disease recur.

Comment. While this patient is receiving cortisone scleroderma cannot be diagnosed either clinically or histologically. Although electrocardiographic ab-

normalities have persisted, there is no evidence that they are due to scleroderma, and they have been regarded as indicating left ventricular strain secondary to arteriosclerosis.

Group II

Case 13. A married woman aged 44 years, first seen in May 1951, stated that for two months she had had painful swelling of the hands and feet, with thickening of the skin of the fingers and inability to grip tightly. At the same time she had developed pains in the wrists, knees, elbows, and muscles of the extremities. She had experienced no vasospastic disturbances. Examination revealed puffiness and generalized swelling of the fingers and inability to close the fist. There was cutaneous oedema over the forearms and legs. The heart was not enlarged, and there was a soft apical systolic murmur. The blood-pressure was 120/80 mm. Hg. No abnormal signs were detected in the remaining systems. The blood count was normal, the erythrocyte sedimentation rate 13 mm. in one hour, and total serum-proteins 7·3 gm. per 100 ml. (albumin 3·3 gm., globulin 4·0 gm.). γ-globulin was 2·03 gm. per 100 ml., thymol turbidity 1 unit, and the thymol flocculation test negative. Plasma-chlorides (as NaCl) were 565 mg. per 100 ml., serum-sodium 335 mg., serum-potassium 18·6 mg. per 100 ml., and blood-urea 22 mg. per 100 ml. Rose's differential sheep-cell agglutination test was negative. The urine analysis was normal. Radiography of the hands, alimentary tract, kidneys, cervical spine, heart, and lungs was normal. Histological examination of a specimen of skin from the left index finger revealed oedema of the corium, homogenization of collagen, and some flattening of the rete pegs. In the course of the next four months, with a low intake of salt and the administration of ammonium chloride, there was no appreciable lessening of the degree of oedema of the extremities. At times the legs were grossly oedematous. Mersalyl given by injection on two successive days did not reduce the oedema.

On September 18, 1951 corticotrophin therapy was instituted, the patient receiving 20 mg. daily by intravenous infusion. Treatment was given on four to six days a week for seven weeks. Two days after the commencement of therapy pain disappeared completely, but on the days on which no treatment was given pain returned. Swelling of the hands and feet diminished gradually, but did not disappear entirely. In the fifth week of hormone therapy *p*-aminobenzoic acid was added in a daily dose of 12 gm. for 10 days, but no appreciable change occurred.

On November 5, 1951 oral cortisone therapy was begun, the patient receiving 200 mg. on the first day and thereafter 100 mg. daily. On this régime she kept relatively free from pain, and swelling of the hands and feet was much less than before. Attempts at reducing the dose of cortisone to 75 mg. daily were constantly followed by a recrudescence of pain and a noticeable increase of swelling. At times she found it necessary to increase the daily dose to 125 mg. for a few days in order to obtain relief. In March 1952, because of the appearance of symptoms suggestive of hypothyroidism, studies of thyroid function were carried out. The basal metabolic rate was —12 per cent., and the blood cholesterol 208 mg. per 100 ml. After a tracer dose of 75μc. of radioactive iodine the uptake at 24 hours was 29 per cent. and the urinary excretion 64 per cent.; the conversion ratio was 10 per cent. Since these figures were at the lower limits of normal, thyroid medication was commenced in a daily dose of three grains. She continued to receive 100 to 125 mg. of cortisone and gr. 3 of thyroid daily till September 1952, when on a visit to the United States she consulted a physician

who reduced the dose of cortisone to 67·5 mg. daily. Pain and swelling in the hands returned, and again improved when the dose was increased to 100 mg. Since then a maintenance dose of 100 to 125 mg. daily has been needed, and she has noticed that if she omits a single dose of cortisone a prompt increase in the pain and swelling of the hands ensues. Examination in September 1953 revealed only slight cutaneous oedema and swelling of the hands, forearms, and feet. The γ-globulin level remained elevated (1·83 gm. per 100 ml.), but the other 'liver function tests' gave normal results. At the time of writing she has been receiving hormone therapy for 30 months, and remains relatively free from pain and swelling.

Comment. While receiving an adequate dosage of cortisone this patient remains relatively free from symptoms, but she relapses on even slight reduction of the dose.

Group III

Case 9. A housewife aged 47 years had been experiencing attacks of coldness and blueness of the hands and feet since 1936. Various forms of treatment had been ineffective. In 1948 a right cervical sympathectomy was performed, resulting in moderate improvement in the denervated limb. In 1950 cervical sympathectomy was performed on the left side; two weeks later the left middle finger became gangrenous and required amputation, but subsequently the attacks of coldness and cyanosis became less severe and occurred less frequently. In 1951 she began to experience pain and stiffening of the fingers, hands, arms, and feet, with breathlessness on exertion, but no difficulty in swallowing. In January 1952 examination revealed generalized skin pigmentation, with several telangiectases on the face, marked flexion deformity of the fingers, and induration, tightness, and thickening of the skin of the fingers, hands, arms, face, and legs. There were several discharging ulcers on the dorsum of both feet. The range of movement of the lower jaw was restricted to one and a half inches. Examination of the heart revealed the presence of mitral stenosis, but a past history of rheumatic fever was not elicited. A blood count was normal, and the erythrocyte sedimentation rate was 35 mm. in one hour. Rose's differential sheep-cell agglutination test was negative. The total serum-proteins were 6·7 gm. per 100 ml. (albumin 3·9 gm., globulin 2·8 gm.); the thymol turbidity was 6·5 units, thymol flocculation +++, and Takata-Ara test negative. Radiological examination showed enlargement of the left atrium; peristalsis in the oesophagus was completely absent; the bones of the hands and wrists were osteoporotic.

On January 23, 1952 corticotrophin therapy was begun in a dose of 15 i.u. subcutaneously at six-hourly intervals. After 18 days, apart from an increase in the sense of general well-being, no subjective or objective improvement had taken place, and the therapy was discontinued. In September 1952 re-examination revealed no change in the patient's condition. The blood-pressure was 120/68 mm. Hg. Radiography showed changes identical with those found previously. A blood count was normal, and the erythrocyte sedimentation rate 30 mm. in one hour. The 'liver function tests' were unchanged. The urine contained no abnormal constituents.

On October 7, 1952 oral cortisone therapy was begun with 300 mg. and 200 mg. on consecutive days, and 100 mg. daily thereafter. By the fourth day pain in the limbs was much diminished, and the range of movement of the lower jaw had increased by approximately half an inch. After 10 days the ulcers on her feet showed signs of healing, and after three weeks had healed completely.

She felt that the tightness of the skin had diminished, but no other change was noted. The 'liver function tests' remained essentially unchanged, the erythrocyte sedimentation rate was still elevated at 26 mm. in one hour, the radiological features were unaltered, and the blood-pressure remained normal.

In mid-January 1953, while still receiving 100 mg. of cortisone daily, she began to experience burning sensations in her finger-tips. Physical examination showed no change. On February 27, 1953, after having received cortisone for 20 weeks, she stated that the burning in her fingers had become unbearable, and an ulcer was present on the pulp of the right thumb. It was thought that the pain was probably due to ischaemic neuritis. The dose of cortisone was reduced to 75 mg. daily, and nine days later, on March 8, the patient developed a severe headache, followed by an epileptiform seizure. Examination on the following day showed no change other than the presence of hypertension, the blood-pressure being 200/110 mm. Hg. The dosage of cortisone was thereupon reduced to 50 mg. daily, and the patient admitted to hospital. During the next week the blood-pressure remained persistently elevated, the diastolic level varying between 100 and 120 mm. Hg. On March 15 she developed severe upper abdominal pain, diarrhoea, and vomiting, the vomitus having a 'coffee-ground' appearance. There was generalized abdominal tenderness and guarding. The urine contained albumin and granular casts, and the specific gravity was 1,015. Twenty-four hours later the blood-pressure had fallen to 60/30 mm. Hg, and a state of shock had developed. There was complete anuria, and the blood-urea was 90 mg. per 100 ml., the sodium, potassium, and chloride levels being slightly below the lower limits of normal. To combat shock intravenous fluid therapy was instituted, the daily dosage of cortisone was increased to 300 mg., given by intramuscular injection in three doses, and in addition 60 i.u. of corticotrophin daily and 4 mg. of *l*-noradrenaline bitartrate ('levophed') per litre were added to the intravenous infusion. Within 24 hours the blood-pressure had risen to 140/90 mm. Hg, but anuria persisted, and the blood-urea had increased to 130 mg. per 100 ml. The above therapy was continued for a further 24 hours, with no improvement in the patient's condition. The anuria and the vomiting of 'coffee-ground' material persisted, although diarrhoea had ceased. The blood-pressure rose to 190/100 mm. Hg. Intravenous fluid therapy was thereupon discontinued, and an intragastric feeding régime was instituted (Bull, Joekes, and Lowe, 1949). Cortisone was reduced to 75 mg. thrice daily, and corticotrophin changed to 20 i.u. by intramuscular injection at six-hourly intervals. In the course of the next four days the blood-urea increased to 300 mg. per 100 ml., and the patient became stuporose and disorientated, and passed into coma. She died one week after the onset of the acute abdominal episode.

Necropsy revealed acute, superimposed on chronic, pancreatitis. The kidneys showed the features of lower-nephron nephrosis. The gastrointestinal tract showed congestion attributable to uraemia, but owing to post-mortem changes it was not possible to assess the degree of sclerodermatous involvement. The heart showed stenosis of the mitral valve. The brain was oedematous.

Comment. This patient did not improve on the initial treatment with corticotrophin, but this may have been due to inadequate dosage. She obtained slight subjective and objective improvement from cortisone, but during treatment developed a fatal illness which was thought not to be directly related to the scleroderma or the therapy.

Case 10. A male clerk, aged 23 years, began to experience swelling of his hands in June 1951, with impairment of his ability to form a tight fist, and pains

in the joints of the fingers. About three months later he began to have generalized pains in the joints, and a sensation of stiffness in the legs and feet. At the same time he noticed that his fingers and toes became blue and cold during cold weather. In November 1951 examination revealed thickening of the skin of the hands, forearms, and legs, cutaneous oedema, weakness and limitation of the grip, and fingers which were cold and blue. The blood count and erythrocyte sedimentation rate were normal. The total serum-proteins were 7·5 gm. per 100 ml. (albumin 4·7 gm., globulin 2·8 gm.); thymol turbidity was 6·5 units, thymol flocculation +++, and the Takata-Ara reaction +. Rose's differential sheep-cell agglutination test was negative. The radiological appearances of the skeleton, soft tissues, chest, and alimentary tract were normal. Histological examination of a specimen of skin from a finger revealed changes compatible with early scleroderma, consisting of oedema of the corium, some increased density of collagen with homogenization in the sub-papillary area, and marked hyperkeratosis.

On November 14, 1951 corticotrophin therapy was begun with 80 i.u. daily in four doses by intramuscular injection. Four days later the patient felt well and was practically free of pain, but objectively there was no noticeable change. On November 24 the dose of corticotrophin was reduced to 60 i.u. daily in four doses. Two days later pain in the joints returned; the dose was thereupon increased to 100 i.u. daily, and this dosage was continued for five days, with prompt relief of pain. Corticotrophin was gradually reduced to a maintenance dose of 30 i.u. daily, given in two doses, and thereafter continued for a period of six months. The patient remained free from pain, but there were no objective changes, and the 'liver function tests' and histological appearances of the skin remained essentially unaltered. In July 1952 he again began to experience generalized joint pains. Long-acting corticotrophin (gel) was started in a dose of 40 i.u., given intramuscularly once daily, but no improvement ensued. Testosterone propionate, 25 mg. daily by intramuscular injection, was given in addition, but failed to prove of benefit and was discontinued after six weeks. The dose of corticotrophin gel was increased to 60 i.u. daily, and subjective improvement followed. At this stage the pain had disappeared with the exception of persistent pain in the left hip, but no objective signs of improvement could be detected. On January 20, 1953 corticotrophin gel was discontinued, and oral cortisone substituted, in a daily dose of 75 mg. for two weeks and thereafter 100 mg. daily. The same relief from pain was obtained as with corticotrophin gel, but the pain in the left hip persisted and was inexplicable. Radiologically the joint appeared normal. During 1952 and 1953, owing to irregular supplies of the drug, there were three periods, each of about two weeks' duration, during which the patient received no cortisone. On each occasion generalized joint pains recurred within two days of discontinuing the drug, only to disappear promptly when cortisone therapy was resumed.

Comment. This patient has received either corticotrophin or cortisone for 28 months, and during that time has derived moderate subjective benefit. Although no objective improvement has resulted, no discernible deterioration in the sclerodermatous process has taken place during this period.

Group IV

Case 3. A housewife aged 27 years had had blue hands, fingers, feet, and toes, in cold weather for many years. In 1949 bilateral lumbar and cervical sympathectomies were performed, after which there was marked improvement in the

feet, but no change in the condition of the hands. In 1950 she began to experience tightness and swelling of the skin of the hands and feet. Examination in March 1952 revealed tightness of the skin of the fingers, hands, forearms, face, toes, and feet. The face was 'beak-like', the mouth could be opened to admit only the tips of two fingers, and the eyelids could not be everted. All the fingers were blue, cold, and tapered. Radiologically the alimentary tract, chest, soft tissues, and joints appeared normal. Rose's differential sheep-cell agglutination test was positive. The blood count, erythrocyte sedimentation rate, and 'liver function tests' were normal. Histological examination of a specimen of skin from a finger showed the features of advanced scleroderma.

On April 8, 1952 corticotrophin therapy was begun in a dosage of 20 i.u. by intramuscular injection at six-hourly intervals, and was continued for 10 days with no improvement, whereupon cortisone was substituted in a dosage of 300 and 200 mg. on consecutive days and 100 mg. daily thereafter for 10 days. Again no subjective or objective improvement ensued, yet the differential sheep-cell agglutination test became negative.

Comment. A short trial of both corticotrophin and cortisone produced no subjective or objective improvement.

Relief of pain. Joint pains or deep 'muscle' pains in affected areas, present in all but three patients (Cases 3, 8, and 11), were completely relieved or greatly alleviated in each case. Pain due to ischaemia was not relieved by treatment, and in two patients (Cases 2 and 9) painful ischaemic ulceration of the fingertips developed while they were receiving cortisone.

Increased mobility of affected parts. In advanced cases little or no increase of mobility occurred, but in early cases, where restrictions of movement were not severe, there was marked improvement.

Raynaud's phenomena. In none of the patients suffering from Raynaud's phenomena was there any diminution of frequency or lessening of severity of the vasospastic disturbances. Two patients (Cases 2 and 9) developed painful digital ulcers while receiving cortisone.

'Liver function tests', as previously defined, were abnormal in 10 patients (Cases 1, 2, 4, 5, 9, 10, 11, 12, 13, and 14) before treatment. In one patient (Case 5) these tests gave normal results after treatment with cortisone, in three (Cases 1, 11, and 13) partial improvement occurred, and in the remaining six no significant change was noted.

Blood count and erythrocyte sedimentation rate. In no case was the blood count persistently abnormal before treatment. In four patients the sedimentation rate was persistently elevated before treatment, and in three of these (Cases 2, 5, and 12) it returned to normal during treatment, while in the fourth (Case 9) it remained elevated.

Rose's differential sheep-cell agglutination test was positive before treatment in three patients (Cases 3, 4, and 8), and in two (Cases 3 and 8) it became negative during hormone therapy.

Radiological abnormalities demonstrable in the heart, lungs, oesophagus, gastrointestinal tract, skeleton, or soft tissues before the treatment did not alter while the patients were receiving cortisone or corticotrophin.

Abnormalities of the electrocardiogram present before treatment persisted while the patients were receiving hormone therapy.

Side-effects of cortisone and corticotrophin. Minor side-effects, such as slight to moderate gain in weight, a tendency to rounding of the face, and mild euphoria, were found in all patients. More striking side-effects were seen in several cases. *Glycosuria* occurred in two patients: in one during treatment with cortisone (Case 6), and in the other with corticotrophin but not with cortisone (Case 14). In neither case did glycosuria necessitate altering the treatment. *Hypertension* occurred in two patients receiving cortisone. In one (Case 8) the level returned to normal when the daily dose was reduced from 150 to 100 mg. In the other (Case 9) the rise in blood-pressure was accompanied by an epileptiform seizure, and occurred after the patient had received cortisone for 22 weeks. *Oesophageal ulceration* developed in one patient during cortisone therapy (Case 1), but did not necessitate alteration in hormone therapy.

Deaths. Two of the patients died while under observation. One (Case 2) deteriorated markedly during a period of 10 months after stopping cortisone, and was seriously ill when treatment was resumed, this time with corticotrophin. She failed to improve, and four days later developed bilateral pneumonia, to which she succumbed. Another patient (Case 9) died in uraemia, as described above, and the necropsy findings did not suggest that scleroderma was responsible for her death.

Discussion

From the results it appears that the response of scleroderma to cortisone or corticotrophin varies in degree from striking benefit on the one hand to no effect on the other. In an attempt to ascertain which patients would benefit most from therapy, we have compared the clinical features in Groups I and II (marked or moderate benefit) with those in Groups III and IV (little or no benefit). The following differences are apparent. The average duration of symptoms before treatment was five months in Groups I and II (four patients) and three years in Groups III and IV (10 patients). Since three patients of the latter groups had had symptoms for periods of six months or less, it cannot be said that early treatment is necessarily a guarantee of success. Nevertheless, as no patient with symptoms of more than six months' duration derived more than slight benefit from treatment, early treatment appears to be advisable. Peripheral vascular disturbance was not a feature in any of the patients in Groups I and II, whereas nine of the 10 patients in Groups III and IV suffered more or less severely from such disturbances. Thus four of five patients without peripheral vascular disturbances obtained moderate to marked benefit, whereas of nine patients who had peripheral vascular disturbances none obtained more than slight benefit. While the series is too small to permit statistical comparison, it seems that treatment with cortisone or corticotrophin is more likely to be of benefit in patients in whom scleroderma is not associated with Raynaud's phenomenon. In patients who showed evidence of visceral involvement by

scleroderma no improvement or deterioration of such visceral disease could be detected.

Scleroderma is a disease with a variable, usually chronic, course. Spontaneous improvement in symptoms may occur. It is thus difficult to assess with certainty the effects of therapy on a small group of subjects. In the absence of sufficient cases to allow of alternate patients being placed in a separate control group, the only form of control has been that supplied by temporary withdrawal of therapy in those patients in whom some benefit had been produced. In no case in which benefit occurred was it maintained on withdrawal of therapy. In one patient (Case 13) omission of even one dose of cortisone invariably results in a prompt return of symptoms. Thus cortisone and corticotrophin, though they may control the disease in some cases, have not been shown to effect a cure. As the beneficial effects of continuous therapy, with no evidence of deterioration in the disease, have been maintained for periods up to two and a half years, it is conceivable that by continuing it the progress of the disease may be indefinitely halted.

The most striking beneficial effect observed in the present series was the relief of pain, with the exception of that associated with ischaemia or trophic ulcers. This result has been noted by other observers, who have met with varying success in the treatment of scleroderma by cortisone or corticotrophin, or both. Bayles, Stout, Stillman, and Lever (1950) used corticotrophin for short periods in four patients, and found subjective and objective improvement but no histological changes. Relief of pain was a notable feature, but relapses occurred when therapy was discontinued. Kierland and Hines (1951) treated four patients with cortisone; subjective improvement occurred in all, and objective improvement in three. One patient showed histological improvement. The authors remarked that improvement of joint pains was striking, and that relapse occurred when therapy was discontinued. They mentioned the use of corticotrophin in two further cases without beneficial effects, but commented that the lack of improvement might have been due to insufficient dosage and too infrequent administration. The dosages used were not stated.

In the present series no differences were noted between cortisone and corticotrophin as regards response, except in one patient (Case 9), in whom it is possible that the lack of response to corticotrophin was due to inadequate dosage. Frank and Levitt (1952) treated a patient with corticotrophin, and obtained no improvement. Subsequent therapy with cortisone produced marked subjective and objective improvement, which was maintained on a dosage of 100 mg. daily, but the patient relapsed when the dosage was decreased. Taubenhaus and Lev (1951) reported subjective and objective improvement in a patient treated with cortisone, but the diagnosis remained obvious. Histological improvement, consisting of loosening of collagen bands, was noted. Sharnoff, Carideo, and Stein (1951) treated a sclerodermatous patient with cortisone and corticotrophin, and found considerable subjective and moderate objective improvement. Hypertension developed, and therapy was discontinued. The blood-pressure continued to rise, and the patient became uraemic and died. Necropsy

revealed marked intimal fibrosis of renal arterioles, with almost complete obliteration of their lumina. A few vessels contained occluding thrombotic masses. The authors kept an open mind as to the possible role of cortisone in precipitating death. The terminal illness of this patient was similar to that of Case 9 in the present series. The histological features of the kidneys in the latter case were, however, quite different, organic vascular changes being absent and the features of lower-nephron nephrosis being evident. It was felt that the patient's death was not directly related to either scleroderma or cortisone therapy. Thorn, Forsham, Frawley, Hill, Roche, Staehelin, and Wilson (1950) obtained no improvement in one patient treated with cortisone, and Briggs and Illingworth (1952) had a similar experience in a patient treated with corticotrophin. This patient had also failed to respond to sodium *p*-aminobenzoate or to 4-3-hydroxy-2-phenylcinchoninic acid.

It will be seen that the results of therapy with cortisone or corticotrophin vary from no effect to marked benefit. We have not been able to trace any report of apparently complete restoration to normal as judged by clinical and histological evidence, a result seen in Case 5 in the present series. It is conceivable that more benefit might have been obtained if these hormones had been administered in higher dosage, a result which is now known to occur in some patients severely affected with systemic lupus erythematosus or pemphigus.

The authors express their thanks to the Superintendent of the Johannesburg General Hospital for making available the necessary hospital records, and to Drs. J. Gluckman and H. I. Lurie, who made the histological sections. Mr. Dry, Anatomy Department, Johannesburg Medical School, is thanked for the photographs.

Summary

1. Fourteen patients suffering from scleroderma were treated with cortisone or corticotrophin, or a combination of these hormones.

2. Four patients obtained moderate to marked improvement. In one case there was clinical and histological reversal to normal.

3. Nine patients obtained slight improvement; one patient obtained no improvement.

4. In the patients who showed marked or moderate improvement the duration of the disease before treatment had been less than six months.

5. The best results were obtained in patients who had no peripheral vascular disturbances.

6. In no case was benefit maintained when treatment was temporarily discontinued.

7. Treatment has been continued for periods up to two and a half years, and is being continued longer in patients who have improved, in the hope that progression of the disease may be prevented.

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FIG. 1. Case 5. October 1951. Section of skin from finger, showing hyperkeratosis, epithelial hypertrophy, and density of collagen (haematoxylin and eosin, ×120)

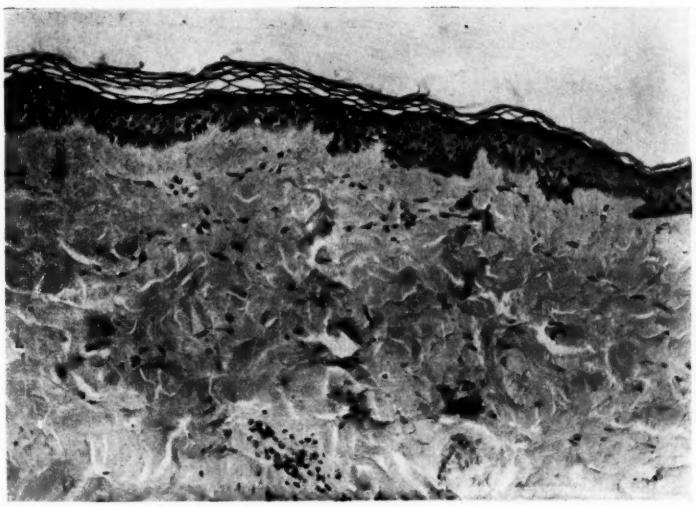

FIG. 2. Case 5. January 1952. Section of skin from an area immediately adjacent to that shown in Fig. 1, showing normal appearances (haematoxylin and eosin, ×120)

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THROMBOANGEITIS OBLITERANS[1]

Clinical and Arteriographic Findings, with a Discussion on Clinical Diagnosis

By G. E. MAVOR

(From Aberdeen Royal Infirmary)

With Plates 22 to 26

When Buerger published his notable monograph in 1908 a distinction, mainly on a pathological basis, was drawn between two types of peripheral vascular disease, thromboangeitis obliterans and arteriosclerosis. Clinical interest was further stimulated in 1924 by the publication of his book on the subject. But a clear clinical concept of the disease was not developed. Age became the yardstick of diagnosis; at one end of the age-scale arteriosclerosis was the degenerative disease and inevitable companion of old age, and at the other thromboangeitis obliterans became the fashionable label. But when lower-limb arterial insufficiency developed in a patient in his fourth or fifth decade the diagnosis remained in doubt, or if it was made it was usually because the patient was not so old as an arteriosclerotic subject should be. So with the passage of years the term 'thromboangeitis obliterans' was widened and acquired a loose clinical application. Though by no means solved, the problem of accurate diagnosis was largely forgotten. A series of 162 cases of peripheral vascular insufficiency in the lower extremity has been studied recently (Mavor, 1953), and the incidence of the four main causes of arterial insufficiency noted.

Analysis of 162 Cases of Peripheral Ischaemia of the Lower Limbs

Aetiology	*Number of cases*
Thrombosis secondary to trauma	4
Thromboangeitis obliterans	6
Atheroma with secondary thrombosis	149
Peripheral arterial embolism	3

Arteriography was undertaken in every case, and the diagnosis based on clinical and arteriographic findings supported by exploration and examination of the main artery of the limb, either femoral or popliteal, and confirmed on occasion by histological examination of involved arterial segments. The six cases regarded as thromboangeitis obliterans were distinct from all the others, and so similar in clinical presentation, arteriographic findings, and microscopic pathology that they were considered to represent a true clinical and pathological

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entity. It is the purpose of the present paper to describe their clinical and arteriographic features, to identify them as cases of thromboangeitis obliterans, and to show that the diagnosis should be limited to such cases.

Details of Cases

Case 1. A man aged 40 years complained of pain in the sole of the left foot on walking. One year ago he had experienced for the first time, on exercise, pain in

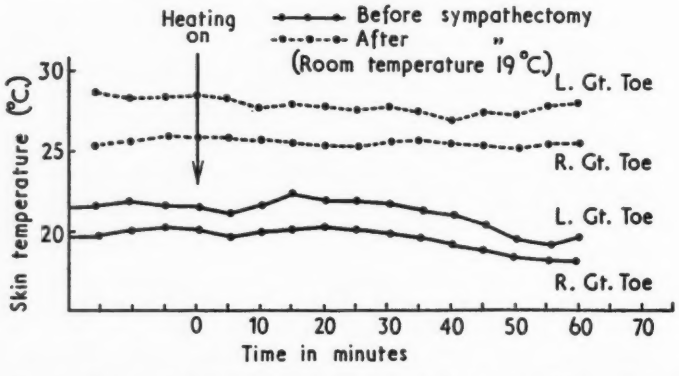

FIG. 1. Case 1. Reflex vasodilatation test. Before sympathectomy the skin-temperature recordings show no evidence of reflex vasodilatation. Recordings after sympathectomy show a rise of about 5° C. in the skin temperature on both sides.

the medial arch of the left foot, radiating to a position under the second and third metatarsal heads. This pain was relieved instantly by rest. At first he could walk about half a mile, but the distance tolerated decreased to 600 paces. After pain began in the left foot he could continue to walk, but was stopped by the development of a similar pain in the right foot, which was first experienced two months ago. He had no calf pain or anterior tibial pain on exercise. Occasionally the left foot felt colder than the right, but this was not a regular symptom. He noticed no pallor of either foot, at rest or after exercise, or any discoloration of the skin. There was no pain during rest. Two and a half months ago he developed some redness and tenderness in relation to the fourth left toe-nail, but this subungual infection subsided in five weeks. There was no history of trauma. He had never noticed a phlebitis, and had no symptoms referable to his upper extremities.

Examination. As regards the legs no skin changes or discoloration, no chronic infection of the toes, and no evidence of peripheral ischaemia, such as pulp atrophy or wasting, were noted. On exercise pallor was more evident in the right foot than in the left; on the right side pallor affected the great toe and adjoining dorsum of the foot, while on the left the great and second toes were pale. Normal colour returned in less than two minutes. Of the peripheral pulses only the femoral could be palpated; they were equal. There were no abnormal pulses. Skin-temperature recordings on heating the trunk showed no evidence of peripheral vasodilatation of the skin vessels, indicating their possible involvement in disease (Fig. 1). The diagnosis of thromboangeitis obliterans was made, the disease being considered more extensive on the left side because of its longer duration and the greater severity of the pain on exercise, although the

more extensive pallor on the right side on exercise was surprising. The absence of anterior tibial pain indicated that, at least in the upper two-thirds, neither anterior tibial artery was involved. Investigations confirmed this clinical impression. Bilateral popliteal arteriograms demonstrated that the disease was more extensive on the left side. On the right side there was a blockage of the posterior tibial artery in the lower third of the leg, where tortuous collateral vessels were beginning to appear. The anterior tibial artery appeared normal (Plate 22, Figs. 3 and 4). The left posterior tibial artery was blocked almost at its commencement, being replaced by numerous tortuous collaterals. The anterior tibial artery was patent as far as the middle of the leg, but below this level it was completely occluded (Plate 22, Fig. 5). In the lower third of the left leg and in the foot none of the normal vessels was recognized, and the whole circulation was carried by collateral vessels (Plate 22, Fig. 6). Biopsy of the left anterior tibial artery and vein revealed a marked degree of periarteritis, making identification difficult. The histological examination showed an artery blocked by thrombus which was undergoing organization and canalization, a finding consistent with the diagnosis of thromboangeitis obliterans (Plate 23, Figs. 7 and 8).

Treatment. Bilateral lumbar ganglionectomy was carried out. This brought about some improvement in the skin circulation in spite of poor expectations from the previous temperature recordings (Fig. 1).

Two years later it seemed that the patient had suffered a further extension of the anterior tibial arteritis on the left side, as he now had pain in the anterior tibial compartment on exercise. The arch claudication had disappeared on the right side; on the left, though still present, it was not of the same severity.

Comment. Within two years the patient had suffered an exacerbation of the disease with evidence of proximal extension of the arteritis. Sympathectomy, though possibly aiding the development of collateral channels, had not altered the course of the disease.

Case 2. A man aged 40 years had had pain in both plantar arches on exercise for 20 years, the right side being always affected more than the left. His exercise tolerance was considerable, and the pain came on only after such exertion as running for 200 yards or climbing stairs quickly. On the right side it started at the posterior end of the medial arch on the sole of his foot, and thereafter he experienced a cramping pain which radiated at times towards the under aspect of the head of the second metatarsal. The pain was relieved instantly by rest. This pain on exercise had become more severe in the past three years, and his tolerance had recently diminished, so that now he could not play golf or badminton.

Examination. As regards the legs the only abnormality noted was a reddened right great toe, the skin and terminal pulp being atrophic. The femoral, popliteal, and anterior tibial pulses were present on both sides and equal. The posterior tibial pulse was felt on the left side, but could not be located on the right. There was no pallor or coldness on exercise. The skin-temperature recordings on heating the trunk showed vasodilatation of the skin vessels, not quite so marked on the right great toe. Right femoral arteriography revealed no arterial disease to mid-calf level. Left popliteal arteriography demonstrated thrombosis of the posterior tibial artery in the lower third of the leg. The anterior tibial vessel was not affected.

Treatment. A right lumbar ganglionectomy was carried out in an endeavour to improve the collateral circulation. Operation on the left side also was

advised, but postponed by the patient, who considered that his symptoms on the left side did not justify such a measure. Three and a half years later it was found that his disease had undergone a natural remission. He now had very slight pain on exercise in the arch of the left foot; exercise caused no pain on the right side.

Comment. This case was interesting in that it showed that thromboangeitis obliterans could remain quiescent over a long period, so that the prognosis was not necessarily bad. During this period the pain on exercise might subside even without treatment.

Case 3. A man aged 26 years complained of the classical symptoms of right-sided arch claudication, of 10 months' duration. Ten years ago he had noticed the onset of typical left-sided arch claudication, and four years ago had first experienced pain in the anterior compartment of the left leg on exercise. These complaints had gradually increased, although for long periods he felt no pain. Ten months ago the left foot began to trouble him less, and the right foot took its place as the site of his chief complaint. Claudication pain in the right anterior tibial compartment and plantar arch had been severe, forcing him to stop work. His exercise tolerance had diminished so that he could walk only 200 yards. There was no calf claudication. He had noticed pallor of both feet, more marked on the left side, and seen only after exercise, but no coldness or discoloration of the skin. There had been several episodes of thrombophlebitis in the long saphenous vein, once diagnosed as a lymphangitis.

Examination. There was no evidence of peripheral ischaemia in the legs at rest. Pallor on exercise was less extensive in the left than in the right foot, where it was intense, amounting to deathly whiteness over the plantar aspect of the sole, the heel, the great toe, and the adjacent dorsum. After resting the pallor faded in four minutes. The femoral and popliteal pulses were felt on both sides. No other peripheral pulses were located. The conclusion was that this patient had a small-vessel arteritis, which had started in the left foot and had extended to the arteries of the lower leg. The disease was now bilateral, and the right side, being more recently involved, was now the cause of complaint, the left side, though more extensively diseased, having developed a good collateral circulation in 10 years. Skin-temperature recordings after reflex vasodilatation confirmed these findings (Fig. 2). A right femoral arteriogram demonstrated normal femoral and popliteal arteries, and thrombosis of the anterior tibial artery at its origin (Plate 24, Fig. 9). The posterior tibial artery showed no filling below the junction of the middle and lower thirds of the leg. The territory of the anterior tibial artery seemed to be mainly supplied by fine collateral vessels from the posterior tibial (Plate 24, Fig. 10). The left popliteal arteriogram yielded almost identical findings. Biopsy of a segment of the long saphenous vein showed it to be closed by a thrombus which was undergoing organization (Plate 24, Figs. 11 and 12).

Treatment. Bilateral lumbar ganglionectomy was carried out. When last seen, a year and a half after operation, the patient's condition was improved. There had been no further exacerbations of the disease, and he had no pain related to the left foot on exercise, although pain in the right foot still caused him to halt. His exercise tolerance had increased sixfold. Both feet were warm and comfortable. Skin-temperature recordings of the feet after reflex vasodilatation (Fig. 2) confirmed these clinical findings.

Comment. The behaviour of the pain on exercise in the left leg indicated that the pain on the right side would continue to diminish, provided the disease

remained quiescent. Although the disease was extensive the collateral circulation was adequate, owing to the young age of the patient at the onset of the disease.

Case 4. A man aged 48 years had first experienced typical pain in the left plantar arch on exercise 14 years previously. Pain was felt along the medial side of the foot and under the first metatarsal head. After three years of this pain the first and second toes of the left foot became bluish and black, and at

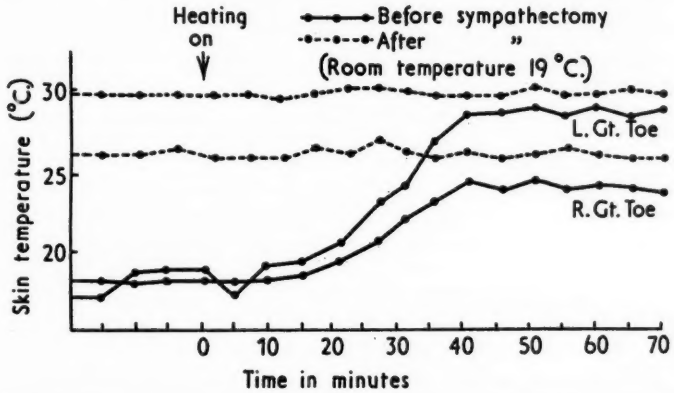

FIG. 2. Case 3. Reflex vasodilatation test. On the left great toe there was a rise in temperature of 12·8° C., while on the right great toe with its poorer collateral circulation the rise was 6·0°; a year and a half after bilateral sympathectomy the increases in skin temperature were maintained.

the Toronto General Hospital East the toes were amputated and a left lumbar ganglionectomy performed. The wounds healed well, and he remained without symptoms until six years ago, when he noted arch claudication in the right foot. The pain was exactly similar to that on the left side. He could walk only 150 paces. One year later his fourth right toe became infected after trauma, and eventually gangrenous. Lumbar sympathectomy was considered, but not carried out. Instead a supracondylar amputation was performed. Three years ago the third and fourth toes of the left foot became discoloured, and then gangrenous. He had never noticed pallor or coldness of his feet, even after exercise. There was no pain when at rest and no history of phlebitis, and he had had no pain on exercise after major amputation restricted his movement.

Examination. The amputation stump of the right leg was well healed. The third and fourth toes of the left foot were gangrenous, and the wound was chronically infected, with cellulitis of the adjacent dorsum. The skin of the dorsum of the foot was smooth and erythematous. The femoral pulses were present and equal. The left popliteal pulse was easily felt, but not the more distal pulses. Popliteal arteriography showed complete obliteration of the anterior tibial artery, and a thrombosis of the posterior tibial at the junction of the middle and lower thirds of the leg. The collateral circulation was extensive (Plate 25, Figs. 13 and 14). Histological examination of a digital artery from an amputated toe showed an organized thrombus in the lumen, the appearance resembling an 'endarteritis obliterans' (Plate 25, Fig. 15).

Treatment. The gangrenous third and fourth toes were amputated. With careful dressing the wounds, which were left open, healed. The patient was under

observation during the next three years. During that time the remaining fifth toe became gangrenous and was amputated, and again with adequate care the wound healed. Fourteen years after the onset of disease in this leg the patient's condition was unchanged, and he had suffered no further exacerbations of the disease. The foot was painless and, in spite of the deformity, serviceable (Plate 25, Fig. 16).

Comment. In this case the disease had run a more fulminating course, although it was extremely doubtful whether major amputation was justified. Superficial consideration might suggest that lumbar sympathectomy had greatly benefited the patient by saving the left leg. This suggestion was, in fact, somewhat misleading, and it was apparent that the course of the disease had not been much altered by sympathectomy.

Case 5. A man aged 28 years complained of pain on exercise in both feet; symptoms were of seven years' duration and most marked on the right side. The pain at the onset was on the medial aspect of the right foot, but radiated as it became more severe towards the heads of the second and third metatarsal bones. Coldness and pallor were also conspicuous, particularly after exercise. Six months after the onset the second toe of the right foot became gangrenous. This toe was amputated, and at the same time a lumbar ganglionectomy carried out. The wound, which was left open, healed without difficulty. Thereafter the pain on exercise in the right foot disappeared. He remained well for two years, and then noticed pain in the left foot on exercise. It was similar to the pain in the right foot, but more variable and not so severe. It was relieved only by rest. The left foot felt cold at times, but this complaint was never so severe as on the right side. A left lumbar ganglionectomy was carried out, and shortly afterwards the pain on exercise in the left foot disappeared. Two years ago he developed an ulcer on the medial aspect of the right great toe. This became grossly infected and extremely painful. In spite of careful dressing and the use of antibiotics it persisted for four months, and then slowly healed. Three months ago the second and third toes of the left foot became gangrenous, and the adjacent dorsum between them ulcerated. The pain associated with this infected area was severe, and remained so. Local treatment necessitated amputation of the second and third toes, and the wound, left open to granulate, healed very slowly. There was no history of trauma or of phlebitis, nor had the patient complained of anterior tibial or calf pain on exercise. For more than 10 years he had suffered from a persistent epidermophytosis affecting both feet.

Examination. There was a granulating wound between the first and fourth toes of the left foot, resulting from the disarticulation of the second and third toes at the metatarso-phalangeal joints. Infection was not severe, and there was no associated cellulitis. Elsewhere the skin of the toes and adjacent dorsum was normal. Of the peripheral pulses only the femoral could be palpated; they were equal. There were no abnormal pulses. Examination for pallor on exercise was not possible. Exploration of the popliteal artery on the right side showed it to be normal, and an arteriogram subsequently carried out showed that the posterior tibial artery was blocked in the lower leg. A network of small vessels replaced the posterior tibial in the distal part of its course. The anterior tibial artery appeared normal. No arteriography was carried out on the left side.

Comment. It was considered that this patient had an extensive bilateral arteritis of the small vessels. It was evident that the disease was having an active course, for in seven years this patient had had five episodes denoting

exacerbations with extension of the arteritis. It was apparent that sympathectomy, though it had aided the collateral circulation to minimize symptoms between attacks, had not affected the course of the disease.

Case 6. A man aged 35 years had suffered from pain in the right foot on exercise for two years. The onset had been sudden, and the pain, on the medial aspect of the right foot, had increased in severity, so that he could now walk only 200 yards without pain. The pain was not altogether characteristic of arch claudication, as it was more generalized and variable, affecting usually the medial side of the foot, often the sole, and occasionally the lateral aspect. Sometimes the pain on exercise radiated to the posterior aspect of the lower leg. There was no anterior tibial or calf pain on exercise. The patient noticed coldness of the right foot, and also considerable pallor, always most noticeable after exercise. There was a history of several small nodules along the medial aspect of the left ankle, possibly suggesting a phlebitis of the long saphenous vein. There was no history of trauma, of local sepsis in the toes, or of infection, and there were no complaints referable to the left leg or foot.

Examination. He was a well-built, healthy-looking young man. At rest there was no evidence of ischaemia in the legs, the terminal pulps and toe-nails being normal, and the skin well-nourished. Of the peripheral pulses only the femoral could be felt. There was no evidence of a phlebitis. After exposure for two hours the skin of the right foot was colder than that of the left, skin-temperature gradients showing a difference of 4° to 5° C. over the toes. Skin-temperature recordings after heating the trunk showed full vasodilatation of the skin vessels on the left side, but a rise to only 28° C. on the right great toe. Pallor on exercise was absent on the left side, but conspicuous on the right side. After exercise to the limit of the patient's tolerance there was extensive pallor of the skin of the right foot: the anterior aspect of the sole was particularly affected as well as the toes, the third toe being quite white. These clinical findings suggested the presence of arteritis of the small vessels, some of the digital arteries being affected, and thrombosis high up in the right posterior tibial artery to account for the pain felt in the lower calf on exercise. The left leg was considered free from disease, not because it was free from symptoms, but because of the absence of pallor of the foot on exercise. Investigations confirmed these conclusions. The right popliteal artery was explored and found to be normal. A popliteal arteriogram showed a normal anterior tibial artery and a large peroneal vessel, but the posterior tibial artery was not filled owing to a thrombus at its origin. The lateral plantar artery was visualized in part of its course, but much of the territory of the posterior tibial artery was supplied by small anastomosing vessels (Plate 26, Figs. 17 and 18). The posterior tibial artery was exposed for biopsy, but the components of the neurovascular bundle were so closely adherent that biopsy was not undertaken, because of the risk of damage to the posterior tibial nerve.

Comment. In this case the arteritis had ascended rapidly to involve the whole posterior tibial artery, and the pain of arch claudication had in consequence become more generalized and less typical. The disease had remained unilateral for two years.

Blood-pressure estimations, analysis of the urine, electrocardiography, estimations of the blood-cholesterol and blood-urea levels, blood Wasserman and Kahn tests, and X-rays of the chest and lower limbs were carried out as a routine in these six cases. The results were normal in every case. There were no

associated diseases apart from those mentioned. One patient was a non-smoker (Case 3), although he had smoked several years previously. All the others had smoked for many years.

Pathology

Buerger's classic pathological studies (1908, 1917) remain the outstanding contribution to the understanding of thromboangeitis obliterans. He described the condition as a disease of the smaller arteries and veins of the lower extremities. It begins characteristically in the small vessels, either digital or plantar, of the foot, and ascends, succeeding vascular segments being affected in each attack. Inevitably the disease becomes bilateral. The anterior and posterior tibial arteries are commonly affected, although their proximal parts may escape (Plate 22, Fig. 5; Plate 24, Fig. 10; Plate 25, Fig. 13). It is extremely doubtful whether large vessels are ever involved. In all Buerger's cases the popliteal artery, when examined, was found to be free from the disease, and in other cases when it was not examined it 'could be felt to pulsate before the operation (of amputation)' (Buerger, 1908). Buerger was at pains to refute the possibility of popliteal thrombosis as the responsible factor in his cases of presenile gangrene.

The histological pattern of the disease is less distinct. It is a non-suppurative, non-specific panarteritis and phlebitis with secondary thrombosis. The latter is the cause of the obliteration of the lumen, and intimal proliferation (von Winiwarter, 1878) plays no role in this (Buerger, 1908). Thrombus propagation in a normal vessel does not occur, probably because of the multiple muscular collaterals available below the knee. The acute phase does not last long, as the changes are quickly obscured by an extensive proliferation of endothelial cells and fibroblasts, the latter affecting the adventitia and to a less extent the intima, leaving the media comparatively free of change. The recognition of an acute arteritis is against the diagnosis of thromboangeitis obliterans, and probably indicates a localized arteritis of 'indeterminate origin' (Learmonth, Blackwood, and Richards, 1944) or a locally advanced example of periarteritis nodosa. The latter disease may affect the large peripheral arteries, but there is little evidence so far to warrant its classification with thromboangeitis obliterans, although it is interesting to speculate that the latter may also be an allergic manifestation, possibly related to persistent infection of the interdigital folds. The histopathology in periarteritis nodosa is very distinctive (Plate 26, Fig. 20) and the best means of making the diagnosis, while in thromboangeitis obliterans it is not distinctive (Plate 23, Fig. 8; Plate 24, Figs. 11, 12; Plate 25, Fig. 15). A further embarrassment to the value of histological examination in diagnosis lies in the possible presence of arteriosclerotic changes in the vessel, although 'the arteriosclerosis is never pronounced except in those rare instances in which the patient has suffered from the disease for many years, and has reached the latter part of the fourth decade' (Buerger, 1917). All of this serves to confuse the picture, and while Kinmonth (1948) stated that 'microscopy of vessels obtained from amputated digits or limbs, or by arteriectomy, is often valuable in

diagnosis', Boyd, Ratcliffe, Jepson, and James (1949) were of the reverse opinion ('little help is gained from studying pathological changes in the vessels'), believing that all the changes described by Buerger could be produced by arteriosclerosis. The comparative absence of change in the media, the absence of endothelial proliferation in the intima, and the absence of an excess of elastic tissue in relation to the internal elastic lamina are the points in Buerger's (1917) histological differentiation of the disease from arteriosclerosis. Generally, in thromboangeitis obliterans, it is impossible to recognize specific histological changes. A representative section cannot always be obtained. The biopsy specimens in the present series were from venous and arterial segments which had been the site of recent acute exacerbations. Nevertheless the microscopic picture (Plate 23, Fig. 8; Plate 24, Fig. 11; Plate 25, Fig. 15) in each case was non-specific, showing little else than an organizing thrombus in a comparatively healthy vessel. It seems clear that the diagnosis of thromboangeitis obliterans can best be made on clinical grounds, where the pattern of the disease is distinct, and that the role of histological examination lies in confirmation. This confirmation usually rests on negative findings, demonstrating the absence of arteriosclerotic changes and of a specific arteritis, and showing thrombosis in a vessel which otherwise looks remarkably normal.

Clinical Features

Thromboangeitis obliterans is a disease of 'very young individuals' (Buerger, 1917), seldom starting after the age of 35 years. In the present series the extremes are 16 and 35 years. The onset may be signalled by the presence of a chronic paronychia, or by a toe becoming wholly or in part gangrenous, the result of digital thrombosis. More often the pain of arch claudication, the classical symptom of thrombosis in the lower posterior tibial or lateral plantar artery, is the first complaint. With local amputation or the control of infection the affected part heals, or in other cases the claudication pain subsides. Collateral channels develop, and may become extensive. The patients are young subjects, in whom 'vascular adaptability is elastic in its scope' (Buerger, 1917). With succeeding attacks exercise pain may spread up to the anterior compartment of the lower leg, or begin in the sole of the opposite foot. Occasionally the lower calf region becomes the site of maximum pain on exercise, indicating thrombosis high in the posterior tibial artery. It appears that the foot in which the disease began is always the more extensively involved, although it may not always be the site of the most severe pain on exercise, as this symptom depends largely on the adequacy of the collateral circulation. Pallor or coldness of the skin may be noticed in the affected foot. This is the result of relative ischaemia, and is always more marked after exercise. There is no good evidence that abnormal tone or spasm of the arteries is a conspicuous feature, and it is certain that pallor on exercise is not due to spasm, and does not represent a 'vasospastic attack' (Kinmonth, 1948; Lynn and Burt, 1949), since it is present after adequate sympathectomy (Case 1). Phlebitis is not uncommon, and occurred in the present series in one case out of six, which is about the usual incidence. In

this case the long saphenous vein, which is the vein usually affected (Buerger, 1908, 1917), was the site of an acute phlebitis of 48 hours' duration. Thereafter the vein did not feel abnormal. The phlebitis can be termed migratory only in the sense that, as in the case of the arteries, different segments may be affected in the course of years.

The periodicity of the disease is a striking feature, attacks varying in intensity and duration. Recurrence may come almost annually (Case 4), or not for many years (Case 3). Whether the disease can become permanently inactive is unknown, but it seems likely that the main vessels represent its upward territorial limit. During quiescence the collateral circulation develops and the patient's symptoms abate. The unpredictable periodicity prevents an accurate prognosis, which, however, is not necessarily serious. This periodicity may indicate that extraneous factors govern the occurrence of exacerbations. The two most commonly implicated are smoking and the presence of fungus infection in the foot. The vascular occlusion produced is complete and permanent. The microscopic vessels which recanalize the thrombus do not do so in a longitudinal fashion, and play no part in restoring the circulation, as they are merely short-circuits between the vasa vasorum. After the obliteration of the normal vessels the nutrition of the lower leg and foot depends on the collateral circulation. This is not a collateral circulation in the true sense of the word, in that the collateral vessels do not by-pass the blocked segment of artery to refill the normal channels beyond, because these have already been occluded in previous attacks. It is rather an alternative circulation, and eventually the whole blood-supply of the lower leg and foot depends on numerous anastomosing small vessels, the outstanding arteriographic feature of the disease (Plate 25, Fig. 14). Gangrene necessitating major amputation, if it does occur, comes very late in the disease, and in the majority of cases, 'in spite of vast and extensive obliteration of arteries and veins, it may be absent' (Buerger, 1917). Thus, while the patient may lose one leg, or perhaps both—and, it is pertinent to add, below the knee, as supracondylar amputation is not indicated—the nature of the disease and its course indicate that he is not in danger of losing his life.

The Diagnosis of Thromboangeitis Obliterans

It has been pointed out that in a limited experience the diagnosis of thromboangeitis obliterans has been most readily made on clinical grounds, and that here at least the disease has a distinct pattern. This is by no means clear from previous studies of the disease, which differ as to the clinical picture presented (Boyd, Ratcliffe, Jepson, and James, 1949; Kinmonth, 1948; Lynn and Burt, 1949; Richards, 1953). It is also difficult to find in the literature adequate criteria of diagnosis, and recently doubt has been cast on the existence of the disease as an entity (Boyd, Ratcliffe, Jepson, and James, 1949). Richards (1953) has described five clinical types of thromboangeitis obliterans, but the difficulties of diagnosis are not resolved, and many cases of arterial insufficiency in the lower extremity could be inaccurately classified under several of his group

headings. The substitution of 'Buerger's syndrome' for 'Buerger's disease' (Boyd, Ratcliffe, Jepson, and James, 1949), while recognizing the variations in clinical interpretation, does not lead to any simplification of the problem. Age, sex, or tobacco-smoking cannot be used as criteria of diagnosis. It is well known that atheroma can commence at an early age, although usually it does not, while 'smoking is an almost universal habit, and, except in diabetics, all forms of obliterative arterial disease are commoner in men' (Richards, 1953).

It seems that there has been an unwarranted tendency to regard thromboangeitis obliterans as an obliterative arteritis of the main vessels, so much so that many recent authorities (Learmonth, 1943–4; Telford, 1943–4; Lynn and Burt, 1949) have made no mention of what may be called the small-vessel type of the disease. This tendency is unsupported by adequate criteria of diagnosis, and it becomes evident that the real problem of diagnosis revolves round the question whether there is such an entity as thromboangeitis obliterans in the main vessels, with its principal symptom of calf claudication. The available evidence seems to be against it. In Buerger's original 11 cases (1908) the femoral and popliteal arteries were not involved. In 1917, in discussing the clinical features of more than 300 cases, his only mention of possible thrombosis of the main vessels was that it may occur very late, as the arteritis and phlebitis spread upward 'until the summit of the organised clot reaches the popliteal or in rare cases the femoral' (Buerger, 1917). Thrombosis of main vessels then may occur (Messent, 1953), but it is a rare and always very late event, leading presumably to the need for major amputation. Boyd, Ratcliffe, Jepson, and James (1949) cast some doubt on main-vessel thromboangeitis obliterans as an entity. It is worth noting that Boyd himself (1938) described a proximal or large-vessel type of the disease, and is quoted by Aird (1949), Richards (1953), and others, but he has since retracted this opinion (Boyd, Ratcliffe, Jepson, and James, 1949), and it is obvious, as he himself stated, that of his 12 reported cases (1938) several were cases of atheroma with secondary thrombosis, while the majority were cases of thrombosis secondary to trauma. Nevertheless Kinmonth (1948) maintained that there is a main-vessel type of the disease, and indeed that the femoral and popliteal arteries may be the initial site of the arteritis. Unfortunately there is little clinical information about his cases, and again it is difficult to be sure of the criteria of diagnosis in each case. It is interesting to note that one patient, who had a popliteal thrombosis and 'no evidence of disease elsewhere', had sustained an injury to his knee in a car accident. Although the diagnosis of traumatic thrombosis was considered, the diagnosis of main-vessel thromboangeitis obliterans was made on the basis of histological examination of a 'small tender cutaneous nodule, which proved to be a focus of thrombophlebitis with changes usually considered typical of thrombo-angeitis obliterans' (Kinmonth, 1948). Kinmonth also printed an arteriogram showing 'Buerger's disease affecting larger arteries'. This illustration shows a segment of femoral artery closed by localized thrombus in the region of the adductor magnus opening, which is the usual site of onset of femoral-artery thrombosis secondary to atheroma; the main artery both proximal and distal to the thrombus is

notably irregular, and this irregularity could be interpreted as due to atheromatous changes. Jones and Steiner (1948–9) offered no clinical criteria for the diagnosis of main-vessel disease, yet described arteriographic changes which were said to be typical of it. Far from being typical of thromboangeitis obliterans, these changes suggest atheroma with secondary thrombosis. Irregularity at the site of the adductor magnus opening should always be regarded as an early atheromatous lesion (Plate 26, Fig. 19). The occurrence of small-vessel arteritis as a clinical entity was confirmed by Boyd, Ratcliffe, Jepson, and James (1949). They preferred the title 'juvenile obliterative arteritis', but clinical and arteriographic evidence shows that the condition was thromboangeitis obliterans as recognized in the present study, or the small-vessel thromboangeitis obliterans of other authors (Kinmonth, 1948; Richards, 1953). Richards (1953) contended that the small-vessel disease is the classic type of thromboangeitis obliterans. Furthermore he stated that in cases which do not conform to the classical picture, presumably those in which main vessels are involved, 'the clinical diagnosis can only be a tentative one'. It is suggested in the present study that the small-vessel disease is not only the classic type of thromboangeitis obliterans, but its only form.

It is apparent from these considerations that calf claudication, which indicates either femoral or popliteal thrombosis, is not a feature of thromboangeitis obliterans. In the present series, of 21 cases of main-vessel thrombosis in patients under the age of 45 years, three or possibly four were cases of traumatic thrombosis, and the remainder cases of atheroma with secondary thrombosis. In an even younger age group it seems that calf claudication is usually the result of traumatic thrombosis. Boyd, Ratcliffe, Jepson, and James (1949) agreed with this conclusion: 'it seems that in most patients under the age of 35 years, the cause of (calf) claudication is traumatic thrombosis and not arterial disease'. With the inclusion of calf claudication in the symptomatology many cases are erroneously diagnosed, and the incidence of the disease greatly exaggerated. Thromboangeitis obliterans is in fact a comparatively rare disease, accounting for six cases out of 162 in the present series; Boyd, Ratcliffe, Jepson, and James (1949) reported eight cases out of 472 cases of peripheral vascular insufficiency affecting the lower limb.

There must remain considerable doubt as to whether thromboangeitis obliterans ever affects the vessels in the upper extremity or elsewhere in the body, notably the visceral or cerebral vessels. Boyd, Ratcliffe, Jepson, and James (1949) stated that apparently 'juvenile obliterative arteritis is confined to the lower limbs, but this is an opinion which may need to be modified in the light of further experience'. There was no involvement of vessels in the upper limb or elsewhere in the six cases described above. Most of the evidence that these vessels may be involved is based on pathological examination, which is at times an uncertain means of diagnosis. In discussing the disease as it may involve the cerebral and visceral vessels, such an authority as Allen (1942) stated that 'for some unexplained reason, the organic changes found in these arteries (cerebral and visceral) are only occasionally inflammatory in origin, and more

commonly are arteriosclerotic in nature'. It is difficult to reconcile such a statement with either a histological or a clinical diagnosis of thromboangeitis obliterans.

Treatment

As regards treatment there is not a great deal to be said. The aetiology of the disease bears no relation to tobacco, which is regarded only as a possible aggravating factor, so that smoking should be avoided. Fungus infection about the toes may likewise activate the disease, and when present requires attention. Many methods of treatment have been tried, but the periodicity of the disease demands a highly critical attitude to any new approach. No improvement is to be expected from limb exercises, which will divert blood to active muscles at the expense of the more important and already ischaemic skin. Nevertheless full movements of the limbs should be practised, if only to maintain mobility of the joints and prevent muscle contracture, particularly flexion-contracture at the knee joint, which may result from the habitual position of hip- and knee-flexion adopted by many patients with severe pain in the foot when at rest. Intermittent venous occlusion may actually decrease and not increase arterial blood-flow (Thompson and Vane, 1951). The various peripheral vasodilators are of benefit, but all have the disadvantage of being transitory in effect and non-selective in action. They may be used during an exacerbation. Pain, for which heroic amputation was once carried out, is often associated with an infected area. This may be a paronychia or an open wound resulting from amputation of a gangrenous toe. Such a wound has to be dressed carefully to maintain efficient drainage. As long as pain is present adequate sedation is required, and it is worth remembering that during sleep considerable peripheral vasodilatation occurs. The infection has to be controlled if deterioration is to be halted, and antibiotics, which can be administered locally or systemically, have increased the speed of healing in patients who suffer from an ulcerated or gangrenous area. Once infection is controlled, and the affected part healing or healed, the pain usually subsides.

Lumbar ganglionectomy is always indicated. It is a rational attempt to improve the collateral circulation, and sympathectomy may minimize symptoms by decreasing the degree of peripheral ischaemia (Figs. 1 and 2). In addition to possible improvement after sympathectomy, if no further exacerbations occur the developing collateral circulation will tend to relieve the patient. On the other hand after sympathectomy the patient's condition may deteriorate if the disease flares up again. Sympathectomy will not arrest the disease, or even materially alter its course. Its benefit lies in diminishing symptoms between attacks. Finally, there is little doubt that any approach other than a conservative one in the matter of amputation is mistaken. With the onset of gangrene, which may involve more than one toe, the prognosis may appear much worse than in fact it is, particularly if the patient is mistakenly considered to have thrombosis in a main vessel, and without justification major amputation may be carried out. This occurred in Case 3. Here the gangrene was undoubtedly the

result of digital thrombosis, and local amputation would have been followed by healing as the acute phase of the disease subsided, as occurred later with the other leg. Even in 1942 Allen stated that 'better recognition, better conservative treatment and less of an impetus toward amputation in many cases, are very desirable'. It can hardly be overstressed that in the great majority of instances amputation is not necessary. When local amputation has to be carried out the toe should be disarticulated and the wound left open to granulate.

As the cause of thromboangeitis obliterans is unknown, treatment remains at the present time entirely palliative. Inability to cure should make one hesitate to diagnose. A clear understanding of the disease is essential for an accurate diagnosis, and much harm can come from an erroneous label. In this regard it is to be noted that, among patients who have thrombosis of a main vessel, the most suitable cases for arterial reconstitution by homogenous grafting are those that are secondary to trauma. These patients are often young, and they have calf claudication. If thromboangeitis obliterans is to continue to be a loose clinical entity, and such patients are mistakenly diagnosed as suffering from the disease, they may be refused the chance of cure by reconstitution of their occluded artery by homogenous grafting, when in fact they represent the most suitable cases of all for reparative surgery.

I wish to thank Mr. G. Gordon Bruce for permission to publish this article, and Professor W. C. Wilson for his advice and criticism in its preparation. I am also indebted to Mr. Alexander Cain for the photography.

Summary

1. Six cases of thromboangeitis obliterans are reported, with arteriographic and histological findings.

2. The diagnosis is discussed, and a limited clinical interpretation of the disease as described by Buerger is suggested, based on the clinical findings in a series of 162 cases of peripheral arterial disease.

3. In the absence of knowledge of the cause of the disease treatment is entirely palliative. The advent of the antibiotics and consequent control of infection have resulted in an improved prognosis, which, however, is still difficult. Lumbar ganglionectomy is always indicated, and conservatism in amputation essential.

4. Thromboangeitis obliterans is an erroneous diagnosis in young patients who have thrombosis of a main vessel, and as such may deny these patients the opportunity of direct reparative surgery for the occluded artery.

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FIG. 3. Case 1. Right side. Lower leg film of a femoral arteriogram, showing normal anterior and posterior tibial arteries

FIG. 4. Case 1. Right side. A further film showing normal filling of the anterior tibial artery, but blockage of the posterior tibial in the lower third of the leg, with small corkscrew collaterals

FIG. 5. Case 1. Left side. The posterior tibial artery is blocked by thrombus at its origin, and the anterior tibial at the junction of the upper and middle thirds of the leg

FIG. 6. Case 1. Left side. Numerous collateral vessels are replacing the normal arterial tree. There is no evidence of the anterior or posterior tibial arteries

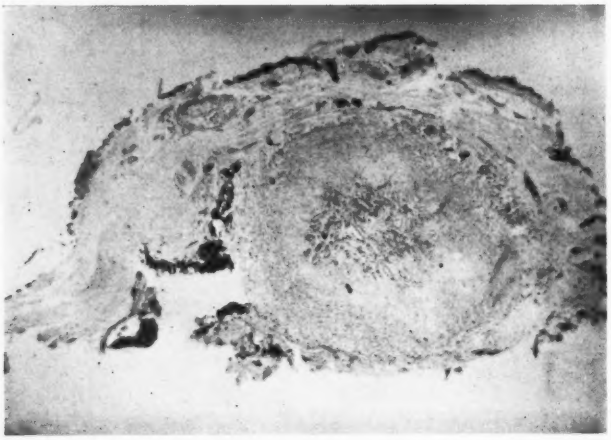

FIG. 7. Case 1. Section of the anterior tibial artery, ×28. The artery is blocked by a thrombus which is undergoing organization and canalization

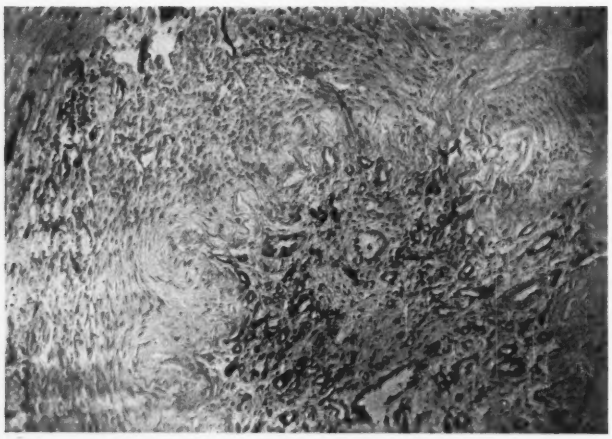

FIG. 8. Case 1. Section of the anterior tibial artery, ×93. There is no evidence of disease of the artery wall. The vessel is blocked by a thrombus which has undergone organization and canalization. These changes are compatible with a diagnosis of thrombo-angeitis obliterans in the inactive phase

FIG. 9. Case 3. Right side. A femoral arteriogram shows normal femoral and popliteal vessels. The anterior tibial artery is closed by thrombus at its origin

FIG. 10. Case 3. Right side. The posterior tibial artery shows no filling below the junction of the middle and lower thirds of the leg. Many tortuous collaterals are present

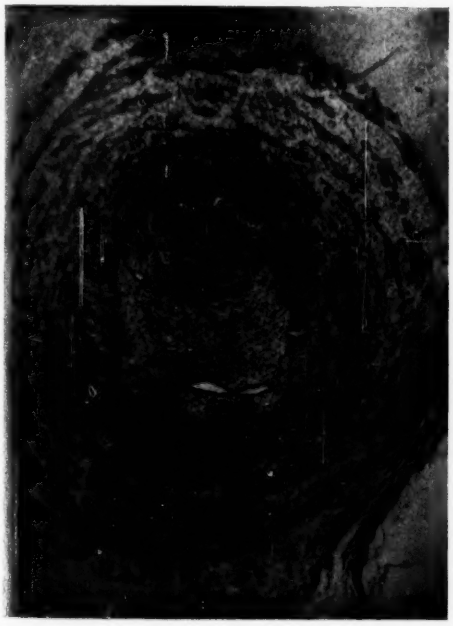

FIG. 11. Case 3. Section of the long saphenous vein at the ankle, ×28. Although biopsy was carried out 12 days after the onset of an acute phlebitis, organization of the thrombus is already advanced

FIG. 12. Case 3. Section of the long saphenous vein, ×93. The thrombus is organized and recanalized to a marked degree. Fibroblastic activity extends discontinuously into the media of the vessel

FIG. 13. Case 4. Left side. The anterior tibial artery is obstructed by thrombus at its origin, and the posterior tibial at the junction of the middle and lower thirds of the leg

FIG. 14. Case 4. Left side. The arteriogram shows an extensive collateral circulation of small vessels entirely replacing the normal arterial tree

FIG. 15. Case 4. Section of the digital artery of a toe, ×28. The appearances suggest an endarteritis

FIG. 16. Case 4. All the toes have been amputated at different times. The foot is healed and entirely useful

FIG. 17. Case 6. Right side. The anterior tibial and peroneal arteries are clearly seen. The posterior tibial artery is obstructed by thrombus at a high level

FIG. 18. Case 6. Right side. The posterior tibial artery is not visualized. Many small collaterals are present over the area of supply of the medial calcaneal and tarsal arteries. The distal portion of the lateral plantar artery remains patent

FIG. 19. A femoral artery showing kinking just above the opening in the adductor magnus. The femoral artery is irregular elsewhere, indicating atheroma

FIG. 20. Periarteritis nodosa. Section of the wall of the radial artery. ×93. There is commencing organization of the thrombus. The arterial wall is normal except for the intense round-cell infiltration of the adventitia

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HYPERTENSIVE CEREBRAL VASCULAR DISEASE AND INTRACRANIAL TUMOUR[1]

A Study in Diagnosis

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With Plates 27 and 28

Patients with arterial hypertension and disease of the cerebral blood-vessels sometimes cause anxiety to their attending physicians because their symptoms resemble those resulting from intracranial tumour. The possibility of hypertensive cerebral vascular disease and intracranial tumour coexisting increases the difficulties of accurate diagnosis. The symptoms or signs which commonly give rise to such anxiety are severe headaches, abnormalities in the fundi, a raised pressure on lumbar puncture or an increased protein-content in the cerebrospinal fluid, the occurrence of fits, and the development of neurological signs with localizing significance.

Patients Investigated

It has been possible to trace the records of 48 patients in whom the signs and symptoms on examination mimicked those of tumours closely enough to gain them admittance to this neurosurgical service. Also included are the records of a further 21 patients who were seen in consultation and investigated, when necessary, without transfer, making a total of 69 hypertensive patients. It is not easy to say how commonly hypertension may closely simulate tumour. Although the present survey covers nearly 16 years, the cases presented are relatively few for the following reasons: no patient was included in the series unless the diastolic blood-pressure was at least 95 mm. Hg; no case was included in which the neurological symptoms and signs were so transient as to make a diagnosis of tumour improbable; and no case was included in which a lumbar puncture had provided evidence of subarachnoid haemorrhage, because the latter event is rarely associated with intracranial tumour. Haemorrhage into the substance of gliomas occurred in less than 4 per cent. of a large series of cases studied by Oldberg (1933), and the occasions on which blood released within a tumour reaches the lumbar subarachnoid space must be few indeed. In order to keep the material reasonably compact, no patients were included in whom signs of a lesion in the posterior fossa predominated. This is not to say that the problem of differentiating hypertension from tumour in the

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posterior fossa is any less acute, although it arises more rarely. Finally, the cases investigated without transfer have mainly been collected during the last three or four years, earlier cases having been lost from memory. Therefore this survey records the clinical features of a series of hypertensive patients who have required neurosurgical surveillance; it does not attempt to indicate how frequently such surveillance is necessary.

Among the hypertensive patients anxiety about the possibility of an intracranial tumour was often made more acute when there were definite abnormalities

TABLE I

Composition of Groups, with Average Ages, Blood-pressures, and Lumbar Cerebrospinal-fluid Pressures

Appearance of retina	*Group*	*Description*	*Number of patients*			*Average age (years)*	*Average blood-pressure*		*Average lumbar c.s.f.-pressure (mm. H_2O)*
			Total	*Male*	*Female*		*Systolic*	*Diastolic*	
Papilloedema, haemorrhages, or exudates	A	Hypertensive cerebral vascular disease	36	23	13	51	217	135	229 (29 patients)
	C	Supratentorial meningioma	30	16	14	45	135	83	302 (14 patients)
	E	Supratentorial intrinsic cerebral tumour (30 gliomata; 2 metastatic cancers)	32	19	13	51	147	87	274 (17 patients)
No papilloedema, haemorrhages, or exudates	B	Hypertensive cerebral vascular disease	33	21	12	59	211	122	171 (29 patients)
	D	Supratentorial meningioma	30	10	20	51	143	84	174 (24 patients)
	F	Supratentorial intrinsic cerebral tumour (29 gliomata; 3 metastatic cancers)	32	21	11	54	135	84	138 (31 patients)

in the fundi. The hypertensive patients were therefore subdivided into two groups. In Group A examination of the fundi had disclosed papilloedema, haemorrhages, or exudates, either singly or in combination. There were 36 such patients, and their symptoms and signs have been compared with those of 62 patients who had retinal changes resulting from the presence of an intracranial tumour. The hypertensive patients in Group B showed either no retinal changes, or no changes other than uneven calibre of the arteries or compression of the veins at the point of crossing of an artery. There were 33 patients in Group B, and their symptomatology was compared with that of 62 patients who had intracranial tumours producing neurological abnormalities without papilloedema. Details of the cases are given in Table I. No case of either hypertension or tumour was included when any reasonable doubt about the diagnosis remained after prolonged observation of the patient or after special investigations (angiography or pneumography was carried out in roughly two-thirds of these patients). An entirely unselected group of cases of intracranial tumour was not possible, because an unselected consecutive series of such patients would not have yielded equal numbers with and without papilloedema. Moreover, if a patient on admission had shown a gross unilateral proptosis, a big hyperostosis, or unmistakable optic atrophy, there would have been every reason to suspect that a meningioma was present. Such cases were accordingly rejected.

Results

Headache. It is now known that raised intracranial pressure alone does not result in headache, and that the headache of brain tumour is due to distortion of the intracranial contents, of which the dura (including falx and tentorium) and the major cerebral blood-vessels have been shown to be capable of producing pain (for example, Northfield, 1938; Pickering, 1939; Kunkle, Ray, and Wolff, 1942). There was one instance, among the cases of tumour analysed here, of headache (which was a prominent symptom) occurring only after an epileptic attack, suggesting that it was due to changes in the cerebral blood-vessels; such changes are known to occur during and after epileptic discharges (Penfield, 1954). A few of the hypertensive patients in the present series were referred to the Unit chiefly because of distressing headache. Although headache was a frequent symptom (88 per cent. among hypertensive patients with retinal changes, and 72 per cent. among those without retinal changes), by itself it seldom justified extensive neurosurgical investigation. It is well known that not all hypertensive patients suffer from headaches. This matter has been discussed recently by Stewart (1953), and his figures show clearly that headaches are not an invariable accompaniment of hypertension. Robey (1931) observed that 218 of 448 hypertensive patients never had a headache, and he produced good evidence that the level of the blood-pressure or of the pulse-pressure was not of necessity linked with the occurrence of headaches. Sutherland and Wolff (1940) described a case in which headache occurring in a hypertensive patient was effectively, though not permanently, relieved by ligation of the superficial temporal arteries. Their observations provide some evidence that headache in a hypertensive subject may arise from extracranial vessels. There are other possibilities, however. The condition designated by Oppenheimer and Fishberg (1928) 'hypertensive encephalopathy', and called by others 'hypertensive crisis', may be a source of headache. In this condition there is oedema of the brain associated with a rise in blood-pressure. This disturbance, when fully developed, may terminate in coma or convulsions. Headache in such cases presumably results from distortion of the blood-vessels or dura, secondary to the oedema of the brain. The difference in the incidence of headache in the two groups of hypertensive patients described here may be due to the greater frequency of cerebral oedema in Group A as compared with Group B. Even in Group A, however, there were only two examples of a clinical history which unequivocally indicated an acute 'hypertensive crisis'.

It is certain that all the factors responsible for headache in hypertension are not yet known; for example, the phenomenon of relief of headache after sympathectomy, even though the blood-pressure is not altered significantly, is still unexplained. Only three patients in the present series had such an operation, and consequently the cases here analysed cannot be used to throw further light on the problem. Whatever the mechanism of the headache, in all the groups of patients described it was such a frequent symptom (Table V) that it was of no value in the recognition of the pathological process underlying their

symptoms. Regarding the quality of headache, careful scrutiny of the records indicates that it is impossible by this means to distinguish the different pathological conditions. Headache in all portions of the skull or in the neck, headache of constant or of throbbing quality, headache that wakes the patient in the night or begins by day, headaches brought on by changes in posture or by worry, have all been recorded in all the groups of patients studied. Provided that papilloedema was not the outstanding retinal abnormality, examination of these cases indicates that headache, however severe, in the presence of hypertension and in the absence of neurological symptoms or signs, never provides good grounds for suspecting a supratentorial intracranial tumour.

Deterioration of vision as a symptom of hypertension or intracranial tumour may arise from papilloedema or retinal arterial disease, from compression or destruction of the visual pathways, or from disturbance of the ocular muscles. In a few cases the patients' complaint of 'not seeing so well' could be ascribed to a disturbance of the language function (that is, from dyslexia). Attacks of amblyopia—often brought on by a change in posture—which may be a sequel of the papilloedema resulting from intracranial tumour, were not noted among these hypertensive patients. In Table V it will be seen that 84 per cent. of the hypertensive patients with retinal changes (Group A) complained of trouble with vision, whereas only 25 per cent. of those without retinal changes (Group B) did so. Part of this difference may have been due to the changes in the fundi among the patients in Group A. As might be expected, it was sometimes possible for the examiner to say that the appearances of the fundi were suggestive of hypertensive retinopathy on the basis of copious haemorrhages and exudates, especially when these were widely scattered over the retina, or when they were disproportionate to the degree of papilloedema.

The changes in the retinae observed in the patients comprising Group A may be broadly divided into cases in which definite papilloedema accompanied widespread haemorrhages and exudates, those in which papilloedema existed alone without convincing evidence of arterial retinopathy (this was the smallest group), and those showing haemorrhages and exudates without definite swelling of the disk. The interpretation put upon these pictures provides a problem over which even experts may disagree. When there is doubt as to whether the appearance of the fundi means raised intracranial pressure, it is usually the practice to seek additional information from the pressure recorded at a careful lumbar puncture. Pickering (1933–4) produced evidence that a high diastolic blood-pressure was linked with an increased cerebrospinal-fluid pressure. Thus, other things being equal, oedema of the nerve-head and retina is likely to occur in patients who have a high diastolic blood-pressure. Table II shows the mean diastolic blood-pressure in 33 of Pickering's (1933–4) patients for whom diastolic and lumbar-puncture pressures are given. The corresponding figures are given for the hypertensive patients (Groups A and B) reported here. The standard deviation of the diastolic pressures is about the same in all groups. It will be seen that the cerebrospinal-fluid pressure of the hypertensive patients with retinal changes (Group A) has a considerably greater standard deviation than

that which occurred in Pickering's series. The greater homogeneity of his cases probably depended upon the examinations being all carried out by the same person using a standardized technique. Probably for this reason it has not been possible to provide definite evidence confirming his findings.

Findings on lumbar puncture. Table I shows the average lumbar-puncture pressures recorded in the several groups. When papilloedema was present and an intracranial tumour was suspected, lumbar puncture has rarely been performed in this Unit. When a lumbar puncture was done before the patient was

TABLE II

Mean Diastolic Blood-pressure and Mean Lumbar-puncture Pressure

Source	*Number of patients*	*Mean diastolic blood-pressure (mm. Hg)*	*Standard deviation*	*Mean lumbar-puncture pressure (mm. H_2O)*	*Standard deviation*
Pickering (1933–4) . . .	33	132	22·6	219	69·0
Present series:					
Hypertensive patients, Group A	29	134	21·2	229	96·7
Hypertensive patients, Group B	29	123	20·0	171	71·4

transferred to the neurosurgical service, it sometimes happened that the available recording apparatus did not measure pressures in excess of 300 mm. H_2O. Probably the recorded pressure underestimated the true pressure in some of the 'tumour' patients. The average level of the cerebrospinal-fluid pressure among the two hypertensive groups was considerably higher than the average level recognized as normal. Thus it seems reasonable to regard some increase in the cerebrospinal-fluid pressure as a consequence of hypertension, though the exact mechanism of this increase is not clear. It follows that, in the presence of hypertension, an elevated pressure disclosed on lumbar puncture does not necessarily imply that an intracranial tumour is present.

Fig. 1 shows the protein levels recorded in the lumbar cerebrospinal fluid in the different groups of patients. Results obtained from blood-stained fluids were discarded from the series. Among the hypertensive patients the protein content of the fluid was frequently below 60 mg. per 100 ml., but it is apparent that a level of approximately 100 mg. per 100 ml. was not uncommon. Indeed, if during the study of a case all the evidence has supported a diagnosis of hypertensive cerebral vascular disease, the finding of a protein level in the cerebrospinal fluid even as high as 200 mg. per 100 ml. does not prove such a diagnosis to be wrong. Very little is known as yet about the mechanism responsible for increased cerebrospinal-fluid protein in hypertension, and the evidence is scanty as to whether such a level can persist for years. A man aged 46 (R.I. 111258) had a total protein of 200 mg. per 100 ml. (confirmed on repeated lumbar puncture). His blood-pressure was 230/150. He then had a bilateral thoracolumbar sympathectomy, and exactly two months after the first lumbar puncture the total protein was 67 mg. per 100 ml. His blood-pressure was now 210/140. Three months later again the cerebrospinal-fluid protein was 70 mg. per 100 ml.

Two years later it was 50 mg. per 100 ml., the blood-pressure still being unchanged. To set against this case there were two instances in the 'tumour' groups of elderly patients who had, in the cerebrospinal fluid, a high initial

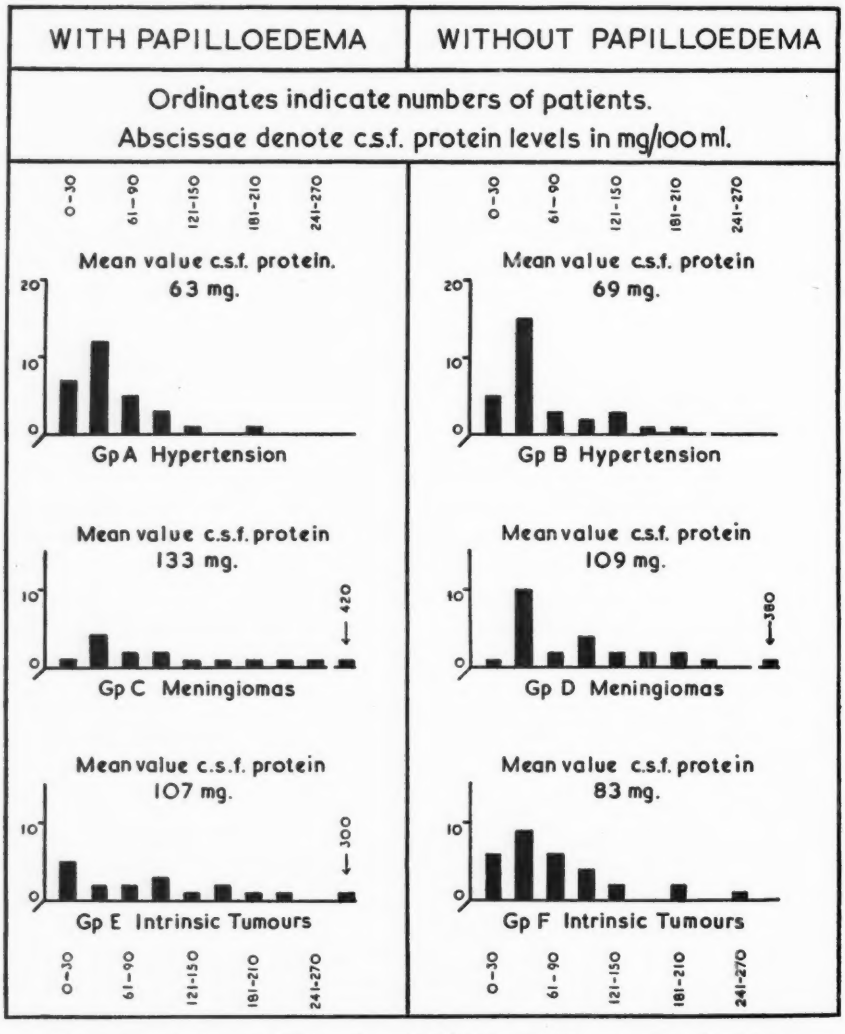

FIG. 1. Protein-content of the cerebrospinal fluid in the different groups of patients.

The abscissa shows protein levels in increments of 30 mg. per 100 ml. Thus the extreme left-hand column in each plot indicates the number of patients with values of 0–30 gm. per 100 ml., the second column those with 31–60 mg. per 100 ml., and so on.

protein level which was found to be higher at a subsequent lumbar puncture. Both patients had meningiomas; the intervals between the protein estimations were two and a half years and four years. Possibly a persistently elevated protein level, or an increase of an existing elevation, is evidence in favour of an

underlying tumour. Further facts about this point are required. Probably such empirical observations will be properly interpreted only when the mechanism of this phenomenon is known. In the present series it has not been possible to obtain an autopsy on a hypertensive patient who had been shown to have a greatly and persistently elevated protein level in the cerebrospinal fluid. Such an examination would be relevant, because an area of softening or infarction

TABLE III

The Incidence and Time of Onset of Epilepsy

Appearance of retina	*Description of group*	*Numbers of patients who had*				*Mean duration of history to admission**	*Mean duration between first fit and admission**
		Fits	*Epilepsy as first symptom*	*Epilepsy among second or third symptoms*	*Epilepsy at any subsequent time before admission*		
Papilloedema, haemorrhages, or exudates	Group A. 36 patients with hypertension	13 (37%)	2	6	4 (and 1 equivocal)	35 months (35 patients)	6 months (13 patients)
	Group C. 30 patients with a meningioma	14 (47%)	11	2	1	24 months (30 patients)	28 months (14 patients)
	Group E. 32 patients with an intrinsic cerebral tumour	17 (55%)	5	4	1 (and 7 equivocal)	17 months (31 patients)	20 months (17 patients)
No papilloedema, haemorrhages, or exudates	Group B. 33 patients with hypertension	15 (45%)	4	9	1 (and 1 equivocal)	31 months (33 patients)	16 months (15 patients)
	Group D. 30 patients with a meningioma	23 (77%)	13	6	1 (and 3 equivocal)	37 months (30 patients)	32 months (23 patients)
	Group F. 32 patients with an intrinsic cerebral tumour	18 (58%)	8	9	1	15 months (31 patients)	12 months (18 patients)

* In the two right-hand columns the moment of 'admission' is the moment of coming under neurosurgical supervision.

close to the ventricle, or on the surface of the brain, might be a source of increased protein. If no such lesion were present, an alternative explanation would be that hypertension might affect the permeability of the choroidal and other intracranial blood-vessels. Another possibility is that an unrecognized endocrine disturbance might indirectly have affected the protein level. Thompson, Thompson, Silveus, and Dailey (1929), for instance, demonstrated a relationship between increased cerebrospinal-fluid protein and myxoedema.

Epilepsy. The occurrence of fits in the presence of hypertension is justifiably a source of anxiety to those attending the patient. Of the present series of hypertensive patients no less than 41 per cent. had a fit at some time in their illness. This incidence is greater than that usually encountered among hypertensive patients, and doubtless follows from the special selection of these cases. Table III indicates the frequency with which fits have occurred in the six groups of patients. The lowest incidence was 37 per cent. among the hypertensive patients with retinal changes (Group A), and the highest was 77 per cent. among patients with meningiomas but without papilloedema. Among the patients with intrinsic tumours who had papilloedema (Group E) the incidence of epilepsy was

uncertain; they not infrequently had episodes which might have represented an epileptic discharge, but which equally might have originated from the effects of raised intracranial pressure. The incidence of the fits among the 'tumour' cases taken as a whole was 60 per cent. (or 56 per cent. if all equivocal cases are omitted). This incidence is higher than that observed by Penfield, Erickson, and Tarlov (1940), or by Lund (1952). Probably the figures recorded here are affected by the unusual composition of the 'tumour' group as regards both the proportion of meningiomas to intrinsic tumours and the proportion of patients with and without papilloedema. Penfield, Erickson, and Tarlov reported epilepsy in 67 per cent. of their patients with meningiomas, and this figure is in keeping with those recorded here. The information in Table III shows clearly that among the hypertensive patients with papilloedema (Group A) such fits as occurred usually took place late in the disease. Indeed among all the groups the average interval between the occurrence of a fit and admission was shortest in Group A, being only six months. This is in sharp contrast with a total duration of illness, for patients in Group A, of 35 months. Similar, though less striking, figures are apparent for the hypertensive patients without retinal changes (Group B). It appears as though initially there had been good grounds for supposing that the hypertensive patients did not have a tumour, but the occurrence of a fit called for a review of the situation, a review which seemed all the more urgent when retinal abnormalities were present. Since not every patient had a fit, the last two columns in Table III have been calculated for different numbers of patients. In parenthesis it is worth observing that both the 'tumour' groups with papilloedema (Groups C and E) have a 'first fit to admission' time which is longer than the 'first symptom to admission' time. This is because, in both groups, patients who began their illness with a fit had the longest histories.

Patients with hypertensive cardiovascular disease can have fits which are just as elaborate and highly organized as those which may result from the effects of cerebral tumour. Two examples will be given; both patients were hypertensive, and neither had significant retinal changes.

A woman aged 48 years (R.I. 102421), with a blood-pressure of 225/150, began six months before admission to have sensory attacks, which consisted of tingling up her left arm to her face. A few weeks later these phenomena were followed by clonic convulsive movements of the left arm. These attacks became gradually more frequent, and two months from the onset the left leg was involved in the process. An angiogram showed an entirely normal vessel-pattern in the involved hemisphere.

A man aged 66 years (R.I. 170179), with a blood-pressure of 190/110, who had not been feeling well for the previous 36 hours, began to experience an irresistible force drawing his eyes to the left. He explained to his wife that he felt as though there were something on his left-hand side which he could not quite see. The following day the adversive phenomena were more prominent, and he had a hallucination of his wife in his left field of vision; he could see lights and cubes on his left, and crowds of people passing from his left upper to his left lower field of vision. The following day he went into a mild status epilepticus, with turning of the head to the left and generalized convulsions.

An encephalogram showed bilateral symmetrical dilatation of the ventricles, as from an atrophic process, and no evidence of tumour. A right carotid angiogram was also entirely normal.

Description of fits in Group A. Among the hypertensive patients with retinal changes (Group A) the following fits were noted. Seven patients had generalized convulsions, and one of them had an episode of confusion and automatism. One patient had focal motor fits beginning in the right arm. Another patient developed a 'leaden feeling' in the left hand, which was followed by loss of consciousness and convulsions. Two patients had episodic automatism only, and in one of them the episodes were associated with aphasia. One patient had a short episode of generalized weakness and numbness, which probably represented an epileptic discharge. Finally, one patient had 'fits' which were insufficiently accurately documented to classify.

Description of fits in Group B. Among the hypertensive patients without retinal changes (Group B) four patients had generalized motor attacks. In one of these four the right side of the body was affected more than the left; two others had also episodes of automatism; one of these began a fit with a smacking of the lips, and subsequently fought for breath and broke into a sweat. The fourth patient had had a preceding episode, presumably an epileptic discharge originating deeply, in which he temporarily and suddenly lost the use of his legs. One patient (described above) had a complicated visual disorder, which ushered in generalized convulsions having an adversive element. Seven patients had focal motor attacks; one of them also had prominent focal sensory symptoms. Unilateral status epilepticus, with or without loss of consciousness, occurred in four of these seven patients. One patient with focal motor attacks also suffered from epileptic discharges involving the visual system of the same hemisphere. These resulted in images or hallucinations in the right homonymous visual field. Two patients had episodes of automatic behaviour.

No uncinate attacks were recorded in either group, nor were any momentary absences or definite attacks of petit mal recorded. Very few minor seizures are recorded among the hypertensive patients. The sample studied is relatively small (28 hypertensive patients with epileptic manifestations), and it is possible that a fuller survey would disclose epilepsies of all types. It seems reasonable to suggest, however, that the pathological abnormalities of hypertensive cerebral vascular disease govern the probable outcome in terms of epilepsy. Indeed, it will be noticed that among these hypertensive patients generalized convulsions were most frequent in Group A, and localized convulsions in Group B. Probably the patients in Group A, who had papilloedema, retinal haemorrhages, and exudates, had patches of oedema and arteriolar necroses in the brain more commonly than the patients of Group B, whose retinae were normal or nearly so. The information about the fits is summarized in Table IV. It is interesting that the hypertensive patients appeared to have a less insistent type of epilepsy. This may be seen from the figures which show the numbers of patients in whom the epilepsy continued up to the time of admission (with or without medication), or in whom the attacks were becoming more severe or more numerous. It seems

that in the presence of a tumour, once an epileptic pattern has been established, the progressive changes associated with the continued growth of the tumour are mirrored by the persistence, and at times by the extension, of the epileptic discharges. In the last column are shown the numbers of patients in whom epilepsy developed after the onset of a definite motor deficit, which varied from a profound hemiplegia or monoplegia to loss of facility in one or more limbs.

TABLE IV

Types and Numbers of Fits Experienced

Description of group	*Number of patients*	*Type of fit*			*Number of fits experienced*				*Number of patients with fits not controlled or becoming more severe*	*Number of patients in whom fits followed a motor deficit*
		Clonic motor	*Sensory*	*Other*	*One*	*Two*	*Three*	*More than three*		
Group A. Hypertension with retina changes	13	9	2	2	4	1	3	5	0	4
Group C. Meningiomas with papilloedema	14	10	6	4	2	1	1	10	4	1
Group E. Intrinsic tumours with papilloedema	17	8	3	10	3	3	0	11	6	0
Group B. Hypertension without retinal changes	15	12	3	6	2	1	2	10	1	2
Group D. Meningiomas without papilloedema	23	19	9	11	2	3	2	16	10	5
Group F. Intrinsic tumours without papilloedema	18	12	5	3	2	2	1	13	8	4

Symptomatology

A survey of the series has shown that the symptoms which are shown in Table V provide useful information, either because they were common to a high proportion of patients in all groups or else because of a striking discrepancy in the proportion affected in the different groups. It should be mentioned that transient symptoms following a seizure were discounted in compiling Table V. Headaches and visual disturbances have already been discussed.

Personality changes and mental deterioration have occurred in a high proportion of all cases. This heading covers a wide range from 'unusual irritability' to 'gross confusion'. It was felt that an attempt to study the mental changes in detail would not be valid without personal knowledge of all the patients in the survey, and without the opportunity of an interview with their relatives. Extensive and persisting mental changes were more often recorded among the patients with intracranial tumours than among those with hypertension.

Vomiting and loss of weight. The occurrence of vomiting had little value in differentiating hypertension from tumour, though of the six groups it was least common among the patients with meningiomas, even when intracranial pressure was raised. As is well known, loss of weight occurs quite commonly in elderly hypertensive patients; from these records it is not possible to say how far loss of weight, when present, was the result of vomiting. It was relatively rare among the patients who had meningiomas with raised intracranial pressure.

There were scattered instances among the 'tumour' patients of a definite gain in weight being recorded as a prominent symptom.

Incontinence did not occur as an isolated symptom. It was least common in the presence of a meningioma, and among the hypertensive patients with retinal changes.

Disturbances of gait and dizziness. A symptom of some importance encountered among the hypertensive patients, and sometimes in patients with the deeper-lying tumours (for example, sphenoid-wing meningiomas or tumours of the basal ganglia), is a disturbance of gait. Since hemiparesis may affect the gait, it is not possible satisfactorily to differentiate the mechanism of 'difficulty in walking' when it is recorded in the notes. Some records, however, give a clear description of 'shuffling gait' or 'tottering gait' which was not a part of an obvious lateralized weakness or ataxy. Perhaps associated with this symptom are the 'giddy spells' to which the hypertensive patient seems subject, though 'dizziness' is not an infrequent complaint of the patient with an intracranial neoplasm.

Dyspnoea, palpitations, ankle oedema, and angina pectoris. Symptoms referable to the cardiovascular system occurred, as would have been anticipated, most commonly among the hypertensive patients. It is interesting, however, that the proportion of patients who complained of such symptoms was higher in the group with meningiomas and without papilloedema than in any other 'tumour' group. Some of the percentages given in Table V have been calculated from notably incomplete data, as the figures in parentheses show. They need interpreting with this reservation in mind. On the whole the missing data were evenly scattered, and were not concentrated upon individual records.

When a neurological abnormality was noted among the symptoms it was obviously important to know whether it came on suddenly, whether it was progressive, and whether it had begun to show signs of improvement. The sudden onset of a symptom suggests that a vascular lesion is responsible, and this is generally the case, but sometimes there is another explanation. In the visual sphere a patient may only suddenly become aware of a deficit which has been present for some time.

One patient (R.I. 137794), by suddenly discovering that he had a complete homonymous hemianopia, which was taken to indicate a thrombosis of the posterior cerebral artery, delayed by more than two years the correct diagnosis of a parieto-occipital meningioma.

But a neurological disorder resulting from a tumour may really be of sudden onset. The following case is an example.

A woman aged 51 years (R.I. 102536), who for six months had had headaches and slight clumsiness of her right arm, was awakened in the middle of the night with a severe headache; after falling off to sleep she woke again, this time to find that she could not move her right arm, and that her right leg was paralysed. She was admitted six months after this episode; during those six months she was just able to walk, but the right arm remained almost totally paralysed. Ten days before admission she noticed for the first time some twitching

movements in the right arm. At operation a left frontoparietal meningioma was found and removed.

TABLE V

Symptoms and Objective Abnormalities Observed with Retinal Changes

Figures in parentheses indicate the number of patients in each group whose histories contributed to the result given.

		With retinal changes			*Without retinal changes*		
		Group A Hypertension	*Group C Meningiomas*	*Group E Intrinsic tumours*	*Group B Hypertension*	*Group D Meningiomas*	*Group F Intrinsic tumours*
Symptoms	Headache	88% (34)	83% (30)	97% (31)	72% (28)	77% (30)	71% (31)
	Deterioration of vision	84% (32)	55% (29)	74% (27)	25% (20)	23% (26)	35% (26)
	Personality changes or mental deterioration	82% (28)	86% (22)	100% (31)	96% (29)	96% (26)	90% (30)
	Vomiting	58% (31)	21% (28)	66% (32)	54% (26)	15% (27)	37% (30)
	Loss of weight	50% (20)	9% (22)	48% (23)	37% (16)	23% (17)	26% (19)
	Incontinence	21% (28)	12% (24)	48% (27)	39% (23)	26% (23)	48% (27)
	Dizziness	82% (17)	38% (13)	53% (17)	77% (13)	81% (16)	64% (14)
	Dyspnoea, palpitations, ankle oedema, angina pectoris	70% (20)	10% (19)	39% (18)	76% (17)	56% (16)	9% (11)
Objective Abnormalities	Blood-pressure: systolic > 160 mm. Hg	94% (36)	3% (30)	31% (32)	100% (33)	20% (30)	9% (32)
	diastolic > 110 mm. Hg	83% (36)	0 (30)	16% (32)	72% (32)	13% (30)	6% (32)
	Albuminuria	37% (30)	0 (30)	8% (25)	32% (28)	4% (27)	0 (27)
	Cardiomegaly, irregular pulse, cyanosis, uraemia	87% (30)	0 (28)	10% (31)	81% (26)	17% (29)	13% (30)
	Abnormal pupils or external ocular movements	42% (36)	57% (30)	81% (31)	42% (31)	53% (30)	62% (32)
	Aphasia	23% (31)	30% (30)	75% (32)	34% (29)	31% (29)	45% (29)
	Anosmia	0 (27)	21% (29)	12% (24)	5% (22)	10% (29)	0 (25)
	Papilloedema	43% (35)	100% (30)	100% (32)	0 (33)	0 (30)	0 (32)
	Retinal haemorrhages or exudates	86% (35)	53% (30)	58% (31)	0 (33)	0 (30)	0 (32)
	Visual-field defect	22% (36)	24% (29)	55% (29)	21% (28)	30% (30)	50% (32)
	Paresis	58% (36)	87% (30)	97% (32)	81% (32)	73% (30)	97% (32)
	Paralysis	8% (36)	23% (30)	9% (32)	19% (32)	33% (30)	59% (32)
	Brisker contralateral reflexes	27% (29)	46% (28)	42% (31)	50% (26)	39% (28)	59% (29)
	Brisker ipsilateral reflexes	0 (29)	15% (27)	13% (31)	12% (26)	21% (28)	20% (30)
	Unilateral extensor plantar response	52% (33)	47% (30)	75% (32)	58% (33)	55% (29)	72% (32)
	Bilateral extensor plantar response	27% (33)	17% (30)	50% (32)	33% (33)	21% (29)	28% (32)
	'Cortical' sensory defect	33% (30)	34% (29)	37% (24)	22% (27)	31% (28)	67% (27)
	Analgesia	9% (33)	0 (29)	28% (29)	10% (29)	7% (27)	39% (31)

Severe fits, either generalized or focal, which are generated by an intracranial tumour, may be followed by a persistent neurological disability. It is tempting to explain such an occurrence on the basis of a vascular accident responsible both for the fit and for the resulting disability. If this is so, it is more likely to result from thrombosis than from haemorrhage, for residual neurological deficits follow epilepsy more commonly than could be accounted for by the known incidence of haemorrhage into brain tumours (Oldberg, 1933).

When a neurological deficit begins to recover, it is tempting to suppose that a tumour is not present. The following was one example to the contrary.

A man of 54 years (Neurosurgical Department No. 3274) began seven months before admission to complain of a peculiar feeling in his head. Mild personality changes next developed, and three months later he returned from work saying that his right arm and leg 'felt funny'. The next day he collapsed on attempting to get out of bed. A few days later he was admitted to hospital. His right arm

TABLE VI

The Pace of the Evolution of Symptoms

Group	*Retinal changes present*			*Retinal changes absent*		
	A (*hypertension*)	*C* (*meningiomas*)	*E* (*intrinsic tumours*)	*B* (*hypertension*)	*D* (*meningiomas*)	*F* (*intrinsic tumours*)
Average interval between first and second group of symptoms	25 months	12 months	11 months	18 months	18 months	11 months
Ditto, after withdrawing from consideration all patients who had a fit as their first symptom	27 months	11 months	5 months	18 months	16 months	9 months

and leg soon became completely paralysed, and he became totally aphasic; he was incontinent. Two months later he began to speak again, and although his right leg remained completely paralysed his right arm improved to the extent that he could shake hands. He also recovered control of his sphincters. In spite of this improvement he was shown to have a malignant glioma in the left hemisphere.

A diagnosis of tumour has sometimes been discredited when a patient recovered from an episode of coma. Ultimate disclosure of a tumour indicated that the coma probably resulted from tentorial herniation, but at the time recovery was taken to mean that a 'stroke' had accounted for the original episode. A progressive neurological disorder, especially when the symptoms and signs can all be related to the same area of the brain, suggests an expanding lesion. But the exact reverse may be the case, and it is not an exceptional experience to be able to link such a disorder with a progressive atrophic process (for example, Davis and Perret, 1946–7). The fact thus remains that it is not possible with certainty to differentiate intracranial tumours from other conditions by the features of the history alone.

The time factor in the evolution of symptoms. The pace at which the symptoms develop is of some value in the diagnosis. An estimate of this factor has been arrived at by noting the time-interval between the first and second batches of symptoms. The information is set out in Table VI, which shows that the symptoms progressed more rapidly with intrinsic tumours than with either meningiomas or hypertensive disorders. This table also demonstrates that, among the intrinsic tumours, patients who began their illness with a fit have had a more slowly moving history than those in whom symptoms of raised intracranial pressure or of a neurological deficit were manifested first.

Objective Abnormalities

The objective abnormalities encountered will be found in Table V. This shows that the mere presence of hypertension decreases the probability of any

given patient having an intracranial tumour. The average systolic and diastolic blood-pressures have been set out in Table I. The percentage of patients in each group who had a systolic blood-pressure greater than 160 mm. Hg and a diastolic pressure greater than 110 mm. Hg is shown in Table V. The presence of albuminuria, an enlarged heart, cyanosis, an irregular pulse, ankle oedema, or increased blood-urea greatly increased the likelihood that the patient's illness was the result of hypertension. Inequality, irregularity, or sluggish light-reaction of the pupils, isolated or combined extrinsic ocular nerve palsies, disturbances of conjugate movement (particularly upwards), and nystagmus are all tabulated under the one heading of 'abnormal pupils or external ocular movements'. It is interesting that two-fifths of the hypertensive patients had such changes, and this finding is important because oculomotor disturbances are commonly found with chronic subdural haematomata in elderly patients. In certain cases conclusive differentiation between hypertension with, and hypertension without, a subdural haematoma can only be made by exploratory burr-holes or special X-ray examination, the choice depending upon the circumstances of the case. All the neurological defects, for example aphasia, visual field defects, and motor or sensory deficits, are commonest among patients with intrinsic tumours. This is to be expected, since such lesions offer the greatest likelihood of large-scale interruption of nervous function. It is interesting that, of the three groups showing changes in the fundi, the patients with meningiomas were most likely to present gross weakness (amounting to almost total paralysis) of at least one limb. In the groups showing no significant retinal changes the intrinsic tumours most often produced a gross motor deficit. Such differences may be of diagnostic help in differentiating between intrinsic and extrinsic intracranial tumour. Bilateral extensor plantar responses occurred most commonly among the patients who had intrinsic tumours with retinal changes, the mechanism here being either bilateral extension of the tumour or compression of the midbrain. Many elderly patients with hypertension also had bilateral extensor plantar responses. Among all the groups it was commoner, when the patient had lateralizing signs, for the tendon-reflexes on the affected side of the body to be increased. Among the hypertensive patients with retinal changes the tendon-reflexes were never observed to be increased on the same side of the body as the affected hemisphere; such a phenomenon occurred in one-tenth to one-fifth of other groups of cases. 'Cortical' sensory loss and analgesia were between two and three times as common in patients who had intrinsic tumours without papilloedema, compared with the other groups. Once the possibility of multiple cerebral metastases has been excluded, the presence of bilateral signs, or of signs referable to lesions both above and below the tentorium, may be taken as a strong indication that the basis of the illness is cerebral vascular disease. Naturally this rule applies most forcefully when there is no papilloedema, for in the presence of raised intracranial pressure tentorial herniation may result in the development of false localizing signs.

The features of the clinical examination of the six groups of patients may be summarized by saying that no single set of findings is of absolute value in

distinguishing the effects of tumour from those of vascular disease. The most important differential point lies in the level of the blood-pressure. A high blood-pressure, especially when associated with a big heart or albuminuria, weighted the scales heavily in favour of hypertension as the ultimate cause of all the symptoms. The mode of development of the symptoms and the observed signs are the data employed in deciding whether it is necessary to carry investigations further. But before a ventriculogram or angiogram is indicated electroencephalography and plain X-rays of the skull are desirable.

The Electroencephalogram

Thirty-nine of the hypertensive patients, 54 of those with meningiomas, and 49 of those with intrinsic tumours had electroencephalograms taken. It has

TABLE VII

The Results of Electroencephalography

To indicate the value of electroencephalography in differentiating these cases. For the 'tumour' patients a 'correct' result was scored when the presence of a tumour was recognized, without requiring the differentiation of intrinsic and extrinsic lesions.

	Retinal changes present			*Retinal changes absent*		
Group	*A* Hypertension	*C* Meningiomas	*E* Intrinsic tumours	*B* Hypertension	*D* Meningiomas	*F* Intrinsic tumours
Result:						
Correct	10	15	16	9	22	21
Uncertain	7	8	5	7	3	4
Wrong	2	3	1	4	3	2

been possible to re-examine nearly 90 per cent. of the records. I am grateful to Miss F. M. Taylor and to Miss F. Boselli for their co-operation in undertaking this task. On this occasion the records were read without any clinical information except whether fits had been a recent occurrence and, sometimes, whether it was believed that the intracranial pressure was raised. On this basis an opinion was expressed as to the pathology of any abnormalities which were seen. Table VII lists the results observed. Considerable help in elucidating the pathology was frequently obtained from records taken at intervals of time, although comparison between serial records was occasionally made difficult because of recent epileptic discharges. The results confirm the belief that electroencephalography may provide useful information. In two of the patients with intrinsic tumours it provided a correct diagnosis of the side of the lesion, when clinical observation had suggested a lesion in the opposite hemisphere. On other occasions a clear-cut electroencephalographic focus, indicating a tumour, sustained a previously tentative clinical localization. Suggestive information was sometimes available from the electroencephalogram as to whether the lesion was intrinsic or extrinsic. Probably the particular value of these records in regard to the present problem is best shown by the results in the two 'tumour' groups without papilloedema (Groups D and F). In Group D (meningiomas without papilloedema) there were four patients in whom hypertensive cerebrovascular disease was originally held to be responsible for their symptoms, three more patients in whom definite hypertension coloured the

clinical interpretation, and one who was regarded as having senile arteriosclerotic changes without hypertension. In all eight cases the electroencephalographic records were diagnostic of tumour. Similar results occurred in the group of intrinsic tumours without papilloedema (Group F), though here it so happened that the considerable age of some of the patients was more likely than hypertension to confuse the diagnosis. In this series electroencephalograms were taken from eight patients older than 65 years who had intrinsic tumours; their ages were 66, 66, 67, 69, 70, 70, 72, and 77 years. It is tempting to ascribe neurological disabilities in the aged to 'senile changes', so that it is interesting to learn that the electroencephalogram was sufficiently abnormal to warrant carrying out further investigations in seven of these cases. The record in the eighth case was unhelpful. The changes observed among the hypertensive patients have not constituted a diagnostic group. Sometimes the records have been within normal limits (three in group A, five in Group B); sometimes diffuse or bilateral abnormalities have been found (seven in each group). Bilateral synchronous delta waves were present as the outstanding feature in two records in each group. Considerable asymmetry of the record was seen five times in Group A and twice in Group B. Finally, two patients in Group A and four in Group B had records which were interpreted as indicating that a tumour was present. Among the hypertensive patients it was usually easier to say, in a given case, that there was no electrical evidence of an intracranial tumour, than that the record indicated the presence of hypertensive cerebral vascular disease. The results reported, however, make it clear that electroencephalography is an examination well worth performing on any patient whose illness might be caused by supratentorial intracranial tumour.

Radiological Signs

The X-rays of the skull have been re-examined on two separate occasions to reduce the subjective error in interpreting the films. The writer is indebted to Dr. P. W. E. Sheldon for assistance in this task. It has been possible to trace the appropriate skull X-rays of between 80 and 90 per cent. of patients in all the groups. The films have been examined with particular reference to erosion of the dorsum sellae and to displacement of a calcified pineal gland. Erosion of the dorsum sellae occurred in very nearly one-quarter of the hypertensive patients with papilloedema. In two patients the evidence was doubtful, and the changes may have represented only decalcification of the base of the skull. Decalcification, which is in part a factor of age, does not seem likely to have affected the results much, for the hypertensive patients who had no papilloedema (Group B), who were on average eight to nine years older, showed less than half as many instances of erosion. Fig. 2 (Plate 27) illustrates the sella of a woman of 63 years (R.I. 6814), who had papilloedema, and a pressure on lumbar puncture of 210 mm. H_2O. Her blood-pressure was 160/100. A ventriculogram revealed that she had no intracranial tumour. In further proof of this fact she lived for eight years after the investigations were performed. The ventriculogram also showed that her third ventricle was not much dilated.

This finding is important, for the mechanism of erosion of the dorsum sellae in obstructive hydrocephalus is generally accepted as resulting from the pressure of a ballooned third ventricle (Twining, 1939). The mechanism of the erosion in this case thus remains obscure. Among the 'tumour' cases displacements of the pineal body downwards, and in one case anteriorly, have been included together with lateral shift. Among the hypertensive patients only lateral shift was observed. Table VIII shows the frequency with which erosion

TABLE VIII

Information from X-rays of the Skull

Group	*Retinal changes present*			*Retinal changes absent*		
	A *Hypertension*	*C* *Meningiomas*	*E* *Intrinsic tumours*	*B* *Hypertension*	*D* *Meningiomas*	*F* *Intrinsic tumours*
Erosion of dorsum sellae . .	23%	64%	44%	10%	48%	32%
Displacement of pineal shadow .	15%	42%	37%	4%	21%	55%

The percentage of cases of pineal displacement is calculated on the basis of the total number of X-ray films examined, not as a percentage of the occasions when the position of the pineal body was definitely recognized. Not infrequently the position of the pineal body was 'uncertain'.

of the dorsum sellae and displacement of the pineal body have been observed in the various groups. Among the hypertensive patients with retinal changes the pineal body was displaced on two occasions towards the hemisphere from which the neurological deficit arose, indicating an atrophic process in the affected hemisphere. These two cases have not been included in the calculation necessary to arrive at the figure of 15 per cent. for cases of displacement of the pineal body. Contralateral displacement, in the absence of a tumour, probably indicated oedema of the affected hemisphere resulting from an area of infarction, as Murphy (1954) suggested.

The value of repeating X-ray films of the skull, when the pace of the history allows it, at intervals of 9 or 12 months, has been well shown more than once in the present survey. For example, Fig. 3 (Plate 27) shows how erosion of the dorsum sellae may be observed to develop. Five years elapsed between the taking of the two pictures shown. The patient (R.I. 173886) was a woman, aged 52 years at the time of her second X-ray. She had had fits for eight years, and had been under medical observation for most of that time. Examination finally showed considerable papilloedema and other evidence of intracranial tumour, and she was found to have a big left frontal glioma. It is possible that knowledge of the radiological changes that were taking place might have led earlier to full investigation and appropriate treatment. It is well known that the presence of an intracranial meningioma may be suggested by radiological evidence, such as an endostosis, enlarged and often asymmetrical vascular markings or foramina, and abnormal porosity or sclerosis of bone. More than once in the present series the endostosis has been located on the film only after its demonstration at operation. The other changes have often been helpful in indicating the diagnosis and its pathology; but changes not grossly dissimilar can sometimes be seen when an intracranial tumour is not present, or when there is an intrinsic tumour.

Special Radiological Investigations: Possible Dangers and Results

Angiography was performed on 12 hypertensive patients (two in Group A and 10 in Group B). Only one of these patients had an untoward reaction. He was a man of 65 years, with a blood-pressure of 200/120. After angiography he had for a few days an aggravation of a pre-existing hemiparesis; this was attributed to oedema in the affected hemisphere, exacerbated by angiography. (Among 'tumour' patients temporary potentiation of the focal signs commonly follows angiography, probably on account of increased swelling of the brain.) There are two reasons why only about one-fifth of the hypertensive patients were subjected to angiography. The first is the desire to avoid angiography in a hypertensive patient whenever possible. The second is that, when the investigation is being done to exclude the presence of a tumour, air studies are usually more completely informative. Indeed, the findings on angiography among the hypertensive patients are usually not very helpful. Sometimes the vessels have been observed to be of irregular calibre, suggesting arteriosclerotic involvement. Occasionally there have been slight deviations of the anterior cerebral arteries from the mid-line, an observation which sometimes led to the suspicion of a cerebral tumour. These deviations, when unequivocal, have in reality been associated with asymmetrical lateral ventricles, as has been demonstrated by subsequent air studies. Air studies were performed 21 times in Group A and 17 times in Group B. In Group A the proportion of ventriculograms to encephalograms was 2:1, and in Group B it was 1:1. The larger number of ventriculograms in Group A appears to be associated with the presence of retinal changes, which suggested raised intracranial pressure. A lumbar encephalogram, however, was safely performed on a patient with a lumbar-puncture pressure of 400 mm. H_2O, and on another patient with a pressure of 260 mm. H_2O. In patients who have cerebral oedema from an acute hypertensive crisis lumbar encephalography may be dangerous, for Pickering (1933–4) reported a patient who died with tonsillar herniation shortly after a lumbar puncture, and Scheinker (1948) reported several cases of tonsillar herniation disclosed *post mortem*. In choosing between ventriculography and encephalography the possibility of considerable cerebral oedema must be set against the risk of rupturing an arteriosclerotic vessel with the ventricular cannula. Such an accident did not occur in the present series, but it is not unknown. Lumbar encephalography, by also outlining the surface of the brain, may give valuable information as to the presence of cortical atrophy. Three patients (two of whom were stuporous) died within a week of ventriculography which was succeeded by a decompressive operation. It is debatable whether their disease, the ventriculogram, or the operation contributed most to their death. Thus the figures available in the present series cannot give satisfactory information about the possible ill-effects of these procedures. Occasionally air studies may upset the patient, and certainly one patient in Group B, who had considerable cerebral atrophy and a blood-pressure of 215/120, was noted to be physically less active and mentally more retarded for about 10 days after an encephalogram.

It may be said of the special radiological investigations in hypertensive patients that they carry a greater risk of morbidity, if not of mortality, than in younger subjects without hypertension, but where there is a need to exclude a potentially remediable cerebral tumour these risks are worth taking.

Frequently the air pictures have been abnormal in hypertensive patients. Symmetrical dilatation of the lateral ventricles, asymmetrical or unilateral dilatation of the lateral ventricles, and dilatation of the third ventricle have all been observed. Excess of air over the cerebral cortex has also been seen.

TABLE IX

The Findings on Pneumography in Hypertensive Cerebral Vascular Disease

	Normal ventricular system	*One lateral ventricle enlarged*	*Asymmetrical enlargement of both lateral ventricles*	*Symmetrical enlargement of both lateral ventricles*	*Enlarged third ventricle*
Group A. Hypertension with retinal changes	1	2	6	10	13
Group B. Hypertension with no retinal changes	1	5	1	8	11

Table IX indicates the frequency with which the various deformities of the ventricular system have occurred, and Fig. 4 (Plate 28) illustrates the considerable degree of hydrocephalus which may sometimes be seen in both groups of cases. Such a severe degree of hydrocephalus was seen radiologically seven times (three in Group A and four in Group B). One patient (R.I. 189484) in Group B came to post-mortem examination shortly after observation by the Neurosurgical Unit. A transverse section through the brain (Plate 28, Fig. 5) shows the considerable and relatively selective enlargement of the third ventricle which occurred in this instance. This is so reminiscent of what has been seen in some of the radiographs that it seems likely that a similar state of affairs existed in several hypertensive patients in this series.

Discussion

To analyse the exact means by which correct diagnoses are reached is never easy and, approached in retrospect, is seldom possible. For this reason there has been no attempt here to sift the data in the hope of revealing the 'diagnostic features' of each patient. It is interesting, however, to summarize some of the features which might have been used to differentiate the patients who suffered from hypertensive cerebral vascular disease from the patients with intracranial tumours who were also hypertensive. Thirty-one 'tumour' patients (25 per cent. of the total) had a diastolic blood-pressure of over 95 mm. Hg. Among these 31 patients the diagnosis of intracranial tumour was on 24 occasions either suggested by or strongly supported by the electroencephalograms or the plain X-rays of the skull. In three further patients the electroencephalographic record was sufficiently abnormal to make further investigation desirable, and in one of these patients the cerebrospinal-fluid protein was 300 mg. per 100 ml., a level which was not observed in hypertensive cardiovascular disease. There remained only four patients in whom the X-rays and the electroencephalograms

were either unhelpful or else not obtained. One patient had papilloedema out of all proportion to his hypertension (the blood-pressure was 140/95), indicating that the raised intracranial pressure arose from an intracranial tumour. The other three patients had clinical features, shown in the present study to be of differential value, which may have helped to indicate that an intracranial tumour was present. One man had had fits for years, and these had become progressively worse in the three months before admission. Two further patients had short histories (one of eight months, the other of three months), and they both showed pronounced and rapid deterioration in the period of 10 to 12 days preceding the discovery of the tumour.

The potential value of plain X-ray films of the skull in the diagnosis of brain tumours has long been recognized, and has been stressed here because it is sometimes overlooked. It is equally well known that brain tumours may lead to abnormalities in the electroencephalogram which can be diagnostic, but the possible value of these records in the differentiation of cases such as those considered above is not so generally recognized. Renfrew, Cameron, and Haggar (1953) have recently discussed the contribution that the electroencephalographic records may make to diagnoses among neurosurgical patients. In all such considerations it is necessary to recall that interpretation of these records is as individual a matter as the assessment of the clinical features of a patient by his physician. The clinical examination of the patient, the skull X-ray, and the electroencephalogram can properly be interpreted only in the light of information derived from all of these sources, and in such circumstances the exact contribution made by any one method of approach cannot be accurately assessed.

The experiments of Cushing (1901) demonstrated that an acute increase in the cerebrospinal-fluid pressure would lead to a rise in blood-pressure. This observation can often be made during the emergencies of neurosurgical practice, but there appears to be little information about a possible relationship between chronic hypertension and a long-standing increase of intracranial pressure. Kety, Shenkin, and Schmidt (1948), in a small series of cases of intracranial tumour, showed a remarkable linear correlation between mean arterial pressure, which varied between approximately 80 and 130 mm. Hg, and cerebrospinal-fluid pressure, which varied between 100 and 900 mm. H_2O, the arterial and cerebrospinal-fluid pressure varying *pari passu*. No such correlation was found among the 'tumour' patients in the present survey, but this fact may be ascribable to lack of uniformity in the hospital records. There have been sporadic cases in the experience of this Unit in which arterial tension, which was found to be raised on several occasions before operation, was restored nearly to normal after relief of raised intracranial pressure; usually the differences have not been clear-cut, and it must be admitted that no systematic attempt has been made in these records to collect accurate information on this point. But the possibility that hypertension might not merely be casually associated with an intracranial tumour, but might actually result from its presence, serves to underline the importance of the problems in diagnosis under discussion.

It is worth pointing out that the pathological processes in the hypertensive patients described here are presumably not homogeneous, nor are they all necessarily peculiar to hypertension. Many of the changes depend upon disease of the cerebral blood-vessels, and vascular disease is not always dependent on hypertension. The researches of Byrom (for example, 1954) have provided strongly suggestive evidence about the morbid process involved in acute 'hypertensive encephalopathy', and it is probably safe to regard such changes, when present, as uniform between patient and patient; the difficulty (with reference to the hypertensive patients reported here) arises in assessing how frequently acute cerebral oedema has occurred. Arteriolar necroses, however, as pointed out by Byrom, may be occurring more or less continuously in hypertensive patients. He based this statement partly on the findings of Pickering, Wright, and Heptinstall (1952), who observed arteriolar necroses in the kidneys and suprarenals removed at operation from patients with malignant hypertension, none of whom had had a particularly acute illness. The implication was that if, in relatively chronic cases, such arteriolar lesions were to be found in excised tissues, they would also be present in the other tissues usually involved in this condition, and these include the brain. But whatever the pathological processes involved, the hypertensive cases here described undoubtedly fall into recognizable clinical groups. Indeed, among hypertensive patients, apart from general changes such as widespread oedema of the brain, the detailed pathological processes may well be irrelevant, in the sense that their clinical manifestations depend at least as much upon the total extent and the site of the lesions as upon their nature.

It might be thought that insufficient importance has been attached to the diagnostic value of the changes in the fundi in severe hypertension. Platt (1954), however, in discussing the appearance of the fundus in hypertension, stated that when neurological abnormalities accompany 'neuroretinitis' an intracranial tumour may be regarded as possibly responsible, unless the diastolic blood-pressure exceeds 140 mm. Hg. Nothing in the present series of cases contradicts this remark; but it should be understood that it is based upon statistical probabilities, and very rarely there must be exceptions even to this rule. Again, it might at first sight seem that patients with non-malignant hypertension and arteriosclerosis could frequently be distinguished from those suffering from tumour by characteristic changes in the fundi (for example, uneven calibre of the arteries). Alpers, Forster, and Herbut (1948) made a very careful study of the histological evidence regarding arteriosclerosis in the retina and in the cerebral blood-vessels. Of 100 adults studied *post mortem*, 14 showed no retinal or cerebral arteriosclerosis, six showed retinal arteriosclerosis only, 45 showed cerebral arteriosclerosis without retinal disease, and 35 had combined cerebral and retinal arteriosclerosis. On the basis of the second and the last of these figures they stated that, in the presence of retinal arteriosclerosis, cerebral arteriosclerosis is six times more likely to be present than to be absent. Apart from the fact that in nearly half of their cases cerebral arteriosclerosis was found when the retina was normal, two further considerations must follow.

The first is that retinal arteriosclerosis, recognized ophthalmoscopically on the one hand and histologically on the other, might prove to have a different incidence because of the different criteria applied. Secondly—a consideration even more important for the present discussion—it cannot be said how commonly retinal arteriosclerosis and intracranial tumour may coexist. Indeed, they may not merely 'coexist': they may, in the same patient, both be eloquent. When an arteriosclerotic lesion and a tumour are both above the tentorium, there may be argument as to which process is responsible for each of the observed signs. Consider the example of an elderly patient in whom disease of the cerebral blood-vessels has damaged a relatively small area of the brain, but no overt signs have developed; suppose such a patient now develops hydrocephalus from a tumour in the posterior fossa. Under these circumstances the earlier hemispheral damage may reveal itself in the form of epileptic discharges of a constant focal pattern. Focal epilepsy developing during an illness proved to be due to a posterior-fossa tumour is not exceptionally rare. Such considerations amplify the statement made earlier, that it may be difficult to differentiate the effects of hypertensive vascular disease from those of hypertension complicated by an intracranial tumour lying in any portion of the skull unless all the relevant means of diagnosis are employed.

Conclusions

A study of the above facts and considerations leaves no doubt that a hypertensive patient with symptoms or signs referable to the nervous system requires particularly careful assessment if the correct diagnosis is to be reached. When there is a suspicion of progressive neurological abnormalities or, in the presence of a stationary neurological deficit, a deterioration in the patient's general state, or when there is a suspicion of raised intracranial pressure, a careful examination must be made of the nervous system, of the whole body, and of the urine. Lumbar puncture may be dangerous, and even when it is devoid of risk the findings are sometimes inconclusive. If after all these investigations a reasonable doubt remains as to the diagnosis, an X-ray of the skull and an electroencephalogram should be performed. Sometimes additional and valuable information may be obtained by repeating the electroencephalogram at an interval of even as little as two or three weeks. Even these tests will not provide a certain diagnosis in every case, and it then becomes necessary to outline the brain with air, or to perform an angiogram. Since these last procedures are not free from risk, it is to the patient's advantage that the fullest diagnostic information should be obtained before they are carried out. It is hoped that the analyses of the present series of cases will draw attention to the problems involved in this small but important corner of the field of diagnosis.

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regarding them. In addition I am indebted to several members of the staff of the Radcliffe Infirmary and of Cowley Road Hospital, Oxford, for permission to include data concerning patients who were under their care. The study was made during the author's tenure of a Nuffield Foundation Fellowship.

Summary

1. The symptoms and signs of 69 patients with vascular hypertension have been compared with those of 124 patients with supratentorial tumours (60 meningiomas and 64 intrinsic tumours). Hypertensive patients may come under suspicion of harbouring an intracranial tumour because of severe headaches, abnormalities in the fundi, abnormal pressure or increase of protein in the cerebrospinal fluid, epilepsy, or the development of focal neurological signs.

2. Headaches occurred frequently among all the patients surveyed. The particular features of a headache had no diagnostic value.

3. The hypertensive patients commonly had an elevated lumbar-puncture pressure (mean value approximately 210 mm. H_2O). The protein-content of their lumbar fluid, though often below 60 mg. per 100 ml., occasionally reached 200 mg. per 100 ml. Therefore raised pressure or increased protein in the cerebrospinal fluid is not incompatible with a diagnosis of hypertensive cerebrovascular disease.

4. Fits were usually not the initial complaint among hypertensive patients, yet 41 per cent. of these hypertensive patients had a fit at some time in their illness. Epileptic discharges resulting from hypertensive vascular disease could produce an elaborately organized pattern. The epilepsy of the hypertensive patient was less insistent than that resulting from intracranial tumour.

5. The presence of hypertension, especially when combined with enlargement of the heart or abnormality of the cardiovascular or renal systems, increased the probability of the whole illness being due to hypertension; but cerebral tumour and hypertension sometimes coexisted.

6. Abnormalities of the pupils or of the ocular movements were found in two-fifths of the hypertensive patients.

7. Electroencephalography was of considerable value in diagnosis.

8. The plain X-ray films of the skull of about 85 per cent. of all the patients have been studied. A hypertensive patient may show apparent erosion of the dorsum sellae and, when there is oedema in the affected hemisphere, may show deviation of the pineal gland.

9. The indications for angiography and pneumography, and the results and the possible dangers of these procedures, are described.

10. The conclusion is drawn that no set of symptoms, or of signs, is of absolute diagnostic value in distinguishing hypertensive cerebral vascular disease from intracranial tumour. A proportion of cases remains which demand full investigation in order to define the pathological process at work.

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FIG. 2. Erosion of the dorsum sellae in hypertension. Note that the cortex on the anterior aspect of the dorsum is missing

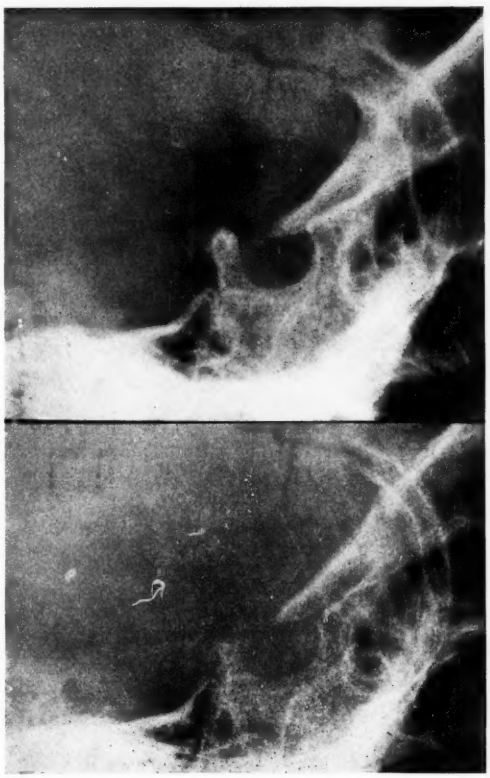

FIG. 3. To show the value of repeating the skull X-ray in the diagnosis of intracranial tumour. In the second film (below) note how the dorsum sellae has become eroded (see text)

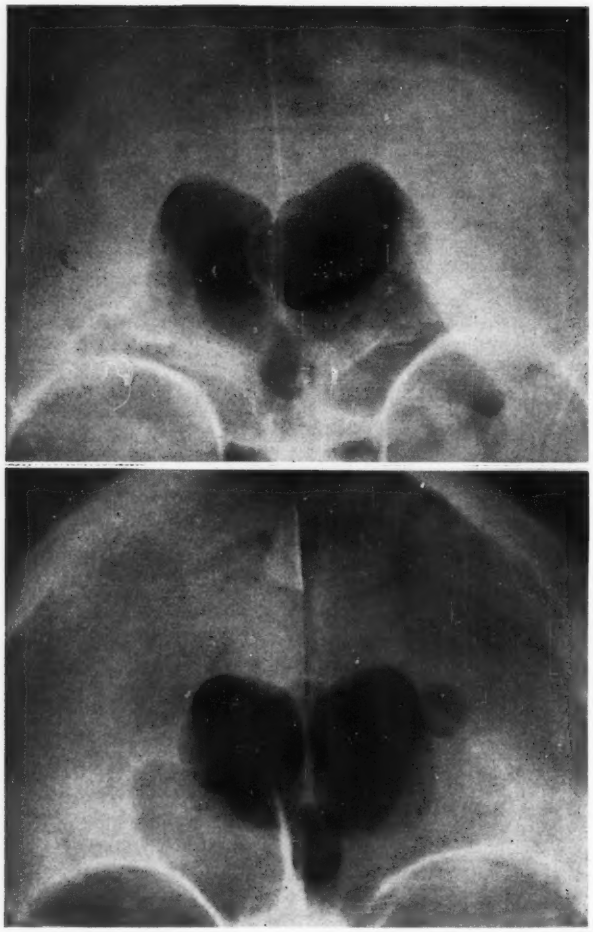

FIG. 4. Above: the ventricular system of a hypertensive patient in Group A. Below: the ventricular system of a hypertensive patient in Group B. Note considerable dilatation of the third ventricle in both instances

FIG. 5. Post-mortem appearance of the ventricular dilatation of cerebral vascular disease. Note the greatly dilated third ventricle

616.33-002-072.5

GASTRIC BIOPSY[1]

A Study of 1,000 Consecutive Successful Gastric Biopsies

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With Plates 29 to 34

Changes in the gastric mucosa have been recorded for many years. One of the earliest observations of importance was that of Samuel Fenwick of London in 1870, who described the gastric atrophy of pernicious anaemia 'in a gentleman about the age of forty-five who died of Addison's idiopathic anaemia'. Fenwick reported that 'the whole glandular structure of the organ was in a state of atrophy'. The less severe changes seen in the different degrees of gastritis, however, could not be satisfactorily described in post-mortem material. It soon became apparent to pathologists, notably Faber (Faber and Bloch, 1900; Faber, 1927, 1935), 'that much of the change could be attributed to post-mortem degeneration, and steps were taken to inject formalin into the stomach immediately after death'. Although this observation resulted in greater accuracy in pathological description, especially of the gastric atrophy of pernicious anaemia (Muelengracht, 1939; Cox, 1943; Magnus, 1937, 1946; Magnus and Ungley, 1938), it was only with the introduction of gastric biopsy that it was possible not only to examine the gastric mucosa histologically under conditions in which autodigestion was eliminated, but also to examine its structure in a variety of circumstances and diseases, and to obtain serial biopsies at intervals in the same patient.

Gastric biopsy was first reported to the New York Academy of Medicine in 1907 by Chevalier Jackson, when he recorded that 'in malignant disease a specimen may be taken with little risk in fungating conditions, but in flat ulcerations suspected of malignancy, the biting out of the edge of the ulcer, though very easy of accomplishment, is unjustifiable'. He had obtained fragments of gastric tumours through his gastroscope, and in 1935 he stated 'the taking of tissue through the open-tube gastroscope is easily done, and hundreds of cases without a single complication have demonstrated its freedom from danger when done with proper precautions' (Jackson and Jackson, 1935). Later Kenamore (1940), Kenamore, Scheff, and Womack (1946), Benedict (1948), and Tomenius (1952) took fragments under direct vision, using modifications of the Schindler flexible gastroscope, an improvement on the rigid tube of Chevalier Jackson. The advantage of taking biopsy fragments under direct

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vision is obvious when local lesions such as ulcer or cancer are concerned; but only a limited portion of the stomach is accessible to the forceps, and the procedure is a formidable one for the patient, besides having a significant morbidity rate. The first biopsy specimens taken blindly through a single-bore flexible stomach tube were obtained by simple suction of the gastric contents, when shed fragments of mucosa were found in the aspirate and identified

TABLE I

The Distribution of 1,000 Gastric Biopsies between 623 Patients

Biopsies per patient	*Number of patients*	*Total number of biopsies*
1	462	462
2	89	178
3	30	90
4	10	40
5	9	45
6	9	54
7	3	21
8	4	32
9	1	9
10	3	30
12	2	24
15	1	15
Total	623	1,000

by microscopic examination. This method was first recorded by Einhorn in 1894, when he described 'erosive gastritis', and later by Hawksley in 1939. Both these writers considered that most of the fragments had separated by natural shedding rather than by true aspiration of a fragment of previously intact mucosa, although Hawksley and Cooray (1948) considered that the latter result might occasionally occur. In 1948 one of us (I. J. W.) independently noticed these fragments of mucosa in the gastric aspirate, and set out with the help of his colleagues to construct an instrument which, with the least discomfort to the patient, would purposely cut off fragments of gastric mucosa of suitable size to permit adequate histological examination, but would not cause undue risk of haemorrhage, perforation, or persistent ulceration (Wood, Doig, Motteram, and Hughes, 1949). The flexible biopsy tube designed at that time has been used, with only minor modifications, throughout the series reported below. A similar or but slightly modified instrument has since been used by several other groups of investigators (Tomenius, 1950; Palmer, 1950; Rubin, Goldgraber, and Smith, 1953).

The present paper reviews our experience of 1,000 successful gastric biopsies performed between April 1948 and January 1953. They were performed on 623 subjects, many of the patients undergoing more than one biopsy (Table I). No criteria of selection were made other than the successful performance of gastric biopsy. The majority of the patients were undergoing investigation or treatment for disease involving the alimentary tract, but some had no apparent gastrointestinal disease. Some biopsies were performed upon members of the staff or medical students attached to the Unit. Of the 1,000 biopsies, 620 were

from male and 380 from female subjects. Considering the different sex distribution of diseases such as peptic ulcer and chronic alcoholism, there were no significant differences between biopsy specimens from the two sexes, and this factor is not mentioned in the subsequent analysis. In 159 instances gastric biopsy was performed after X-ray irradiation of the stomach, usually in the management of duodenal ulcer (Brown, Scott, Holman, Wood, Finckh, Weiden, and Davis, 1952). Since such irradiation is known to produce gastritis (Doig, Funder, and Weiden, 1951; Scott, Holman, and Finckh, 1953–4), these patients, with the addition of one who was treated with intravenous nitrogen mustard before biopsy, have for most purposes been considered separately.

The Technique of Gastric Biopsy

Structure of the flexible gastric biopsy tube. The tube consists of a length of Bowden wire covered by plastic to render it airtight (outer diameter $\frac{1}{4}$ in.). A wire passes from a proximal handle down the length of the instrument to operate a terminal cylindrical knife-blade encased in a stainless steel chamber. This chamber has a lateral hole (diameter $\frac{3}{32}$ in.), through which a fragment of gastric mucosa may be sucked by exerting negative pressure through a lateral inlet at the proximal end of the tube. The overall length of the tube is 100 cm., and depth levels are marked at 45, 55, and 65 cm. from the lateral hole. The fragment of mucosa is cut off by pulling up the cylindrical knife past the lateral hole. A terminal screw in the knife chamber can be removed to allow ejection of the cylindrical blade together with the fragment of mucosa.

Technique of gastric biopsy. Gastric biopsy is performed with the patient fasting. The throat is anaesthetized with a cocaine and adrenaline gargle; then a Ryle's stomach tube is passed into the stomach, with the patient in the sitting position. He is then placed in the prone position, and the stomach emptied completely by elevating the foot of the couch and exerting gentle suction as the Ryle's tube is slowly removed. The gastric biopsy tube is passed into the stomach with the patient lying on his left side. The fact that the stomach has been entered is noted by the length of tube passed (depth 45 to 55 cm.), and if necessary by exerting some downward pressure on the tube, which elicits some discomfort to the patient. The site of this discomfort is a valuable guide to the position of the end of the tube. The fragment of gastric mucosa is obtained by exerting negative pressure with an exhaust pump, and then pulling up the blade to cut off the fragment, which has been sucked into the lateral hole in the knife chamber. The operation is repeated after the instrument has been withdrawn 2 or 3 cm. and rotated 180 degrees. Thus two samples of mucosa may be obtained, and these are removed by disconnecting the terminal screw, ejecting the cylindrical blade, and blowing out the fragments. The fragments are immediately fixed in formol-saline solution. In order to determine the site from which the fragment was usually obtained, several patients have had a biopsy performed two or three days before an interval gastrectomy was done for peptic ulcer. This test revealed that the fragments were usually taken from the body of the stomach; occasionally the antrum was reached,

and this fact was also indicated by subsequent histological examination of the fragment.

After the biopsy the patient rests for at least three hours, a milk drink being given after the first hour. Out-patients are then allowed to return home to rest for the remainder of the day. The time taken for healing of the small crater produced by gastric biopsy in man is unknown, but in the cat Gunter (1950) found that the ulcer produced by this method of gastric biopsy was completely epithelialized in three days.

Histological methods. The biopsy specimens obtained consisted of disks of mucosa usually 2 mm. in diameter. These were embedded in paraffin and sectioned carefully on edge. In 942 instances they included the full thickness of mucosa and a variable, but usually slight, amount of submucosa; in 58 instances, while the specimen was deep enough to give a good indication of the appearance of the mucosa, the deeper portions of the tubules were not included, and it was not possible to assess the thickness of mucosa. Stains used were haematoxylin and eosin, mucicarmine, and a trichrome stain (Motteram, 1951), the latter being used to demonstrate the acid- and pepsin-secreting cells of the tubules.

Complications of gastric biopsy. The only complication observed has been haemorrhage into the alimentary canal: neither perforation nor submucosal gastric haematoma (Palmer and Smith, 1953) have occured in our patients. There were no deaths. Ten patients, five male and five female, showed clinical manifestations of haemorrhage, five within 12 hours and all within 24 hours of the biopsy. The average age of these 10 patients was 49 years (range 18 to 62 years), and the biopsy was performed in the investigation of a variety of illnesses: syringomyelia with severe cystitis, one case; pernicious anaemia with subacute combined degeneration of the cord, two cases; subacute degeneration of the cord without changes in the peripheral blood, one case; asthenia of psychogenic origin, one case; alcoholic hepatitis, one case; clinical gastritis, three cases; no symptoms, but a family history of pernicious anaemia, one case. In only one case was any abnormality of blood-coagulation demonstrated, this patient having a prothrombin concentration of 34 per cent. The histological findings in these patients were as follows: superficial gastritis in one case; severe gastritis with gastric atrophy in six cases; gastric atrophy, typical of pernicious anaemia and subacute combined degeneration of the cord, in three. The clinical symptoms of bleeding were vomiting of blood, usually in small amounts, in seven cases, and melaena alone in three cases. In eight of the 10 patients the symptoms were classified as 'mild', and in two as 'moderately severe'; two required blood transfusions, but one of these patients was a woman suffering from severe cystitis and general toxaemia resulting from syringomyelia, and transfusion had been contemplated before the biopsy; she vomited only a small amount of blood. In her case biopsy was performed because subacute combined degeneration of the cord was suspected. Gastric biopsy is thus a safe method of investigation. Of 1,226 attempted or successful biopsies haemorrhage was observed in only 10 cases (0·8 per cent.), and was of sufficient severity to require

transfusion in only two (0·16 per cent.); there were no other complications, and no deaths. In comparison, Jones, Doll, Fletcher, and Rodgers (1951) reported 75 accidents, with 32 deaths, in 49,000 gastroscopies without gastric biopsy.

Failures. During the course of these 1,000 successful biopsies, attempts at biopsy failed on 182 occasions, and a further 44 successful biopsies have not been included in the series because the histological material was not available for review. The failures were due to various causes. In 76 instances biopsy produced oesophageal and not gastric mucosa, while in 72 instances no specimen was obtained. In the remaining 34 instances the material was either insufficient to permit histological diagnosis or spoiled during embedding or the cutting of sections. This overall failure rate of almost 20 per cent. does not give a true picture of the present efficacy of this method of gastric biopsy. Many of the failures occurred early in the series: in the first 100 attempted biopsies the failure rate was 39 per cent., and in the last 300 less than 8 per cent.; the present (1954) incidence of failure is about 5 per cent. Sixty-three of the 182 failures occurred when gastric biopsy was attempted immediately after gastroscopy. At gastroscopy the stomach is inflated with air, so that gastric mucosa is less likely to be obtained by a suction technique. Finally, the 182 failures occurred in 150 patients. The attempt at biopsy was not repeated in 64; of the remaining 86 a further attempt was successful in 84. Gastric biopsy by the present technique is therefore an efficient method of obtaining specimens of gastric mucosa for histological examination.

Histological Findings

In 726 instances two pieces of mucosa were obtained on the same occasion from different portions of the body of the stomach, and in 536 (73·8 per cent.) of these cases the appearances in the two pieces were very similar. In 190 instances (26·2 per cent.) there were considerable differences between the two pieces, and in these cases it appeared that the gastric changes were patchy. The thickness of the mucosa was measured by means of an eyepiece micrometer, the mucosa being taken to end at the tips of the tubules or, where tubules were absent, at the inner side of the muscularis mucosae. To assess the average thickness of varying types of mucosa, only those specimens which included the full thickness of mucosa were used; this was done in full cognizance of the possibility that more specimens were rejected where the mucosa was thick than where it was abnormally thin.

The variation in histological appearance was considerable, depending largely on the degree of inflammatory cell infiltration and the degree of atrophy of the tubules. In 167 instances the surface epithelium was composed of regular tall columnar cells, the pits were short and narrow, and the tubules were regular, straight, and almost entirely composed of normal acid- and pepsin-secreting cells. The substantia propria of the mucosa contained only very occasional lymphocytes, plasma cells, or fibroblasts (Plate 29, Figs. 1 and 2). Such mucosa was considered to be entirely normal; the average thickness was 0·54 mm.

In 178 instances the appearances of the mucosa were entirely similar except for the presence of small numbers of plasma cells or polymorphs in the most superficial portions of the substantia propria (Plate 30, Figs. 3 and 4). These appearances were described as 'slight superficial gastritis'; the average thickness was 0·54 mm. In 253 instances the mucosa was of similar thickness (average 0·52 mm.); the tubules were composed of normal numbers of acid- and pepsin-secreting cells, but the superficial portions of the substantia propria contained considerable numbers of infiltrating cells. In 104 of these specimens the infiltration was composed of both polymorphs and plasma cells, and the surface epithelium was often irregular or flattened, and showed penetration by polymorphs (Plate 30, Fig. 5). In the remaining 149 specimens in this group the infiltration was almost entirely composed of plasma cells, and the surface epithelium was usually normal. These appearances were described as 'moderate superficial gastritis' or 'severe superficial gastritis', according to the severity of the cellular infiltration. The presence of polymorphs was taken to indicate a more active phase of the condition.

A slightly more severe change was seen in 125 instances, in which the cellular infiltration of the superficial portions of the substantia propria was accompanied by some reduction in the size of the tubules. The tubules tended to be tortuous, and were often composed of considerable numbers of pale cells which did not stain like acid- and pepsin-secreting cells with the trichrome method. The infiltration of the substantia propria was again mainly composed of plasma cells; in 52 specimens polymorphs were also present in significant numbers. These biopsy specimens were considered to show 'moderate or severe superficial gastritis with some atrophy'; the average thickness of mucosa was 0·47 mm.

In 128 specimens the changes were more severe. In general the mucosa was moderately or considerably reduced in width. There was widespread infiltration throughout the substantia propria with plasma cells, lymphocytes, and at times polymorphs, the latter often occurring in patches (Plate 31, Figs. 6 and 7). The surface epithelium was in some cases flattened, and in others partly composed of tall goblet cells which stained deeply for mucin. Similar goblet cells were often found in the pits, which tended to be elongated and dilated (Plate 32, Fig. 9). The tubules were considerably atrophic; they were reduced in amount, and often many of the cells comprising them failed to stain for acid and pepsin (Plate 32, Figs. 10 and 11). The most severe examples in this group comprised a narrow mucosa, irregular and often goblet-cell epithelium on the surface and in the pits, small irregular tubules largely composed of 'non-specific' cells, and diffuse infiltration of the substantia propria (Plate 32, Figs. 9, 10, 11). The specimens in this group were considered to show 'atrophic gastritis'. Even more severe atrophic changes were seen in 93 instances. In these the mucosa was considerably reduced in width, the average being 0·43 mm. Although they were not always present, goblet cells often comprised considerable portions of the surface epithelium or pits (Plate 33, Figs. 12, 13, 14). The tubules were greatly reduced in amount and tortuous; usually only a few cells stained for acid and pepsin with the trichrome method (Plate 33,

Fig. 14). The superficial portions of the mucosa were often partly villous (Figs. 13 and 14), and the degree of cellular infiltration of the substantia propria was often only moderate. In 39 instances less severe changes were also seen in the same specimen, indicating some patchiness; in the remaining 54 specimens the changes were uniformly severe. These specimens were grouped as 'severe atrophic gastritis'.

In the remaining 56 biopsy specimens the appearances differed still more from the normal mucosa of the body of the stomach, and in fact resembled

TABLE II

The Histological Findings in 1,000 Gastric Biopsies

Histological findings	*Number of biopsies*
Normal	167
Slight superficial gastritis	178
Moderate or severe superficial gastritis	253
Superficial gastritis with atrophy	125
Atrophic gastritis	128
Severe atrophic gastritis	93
Gastric atrophy	56
Total	1,000

the mucosa of the intestine rather than of the stomach (Plate 34, Figs. 15 and 16). The mucosa was considerably reduced in width (the average being 0·42 mm.), but often villous. The epithelium of the surface and the pits was almost entirely goblet-cell in type. The pits usually ended blindly, often having Paneth cells at their bases; a few ended in small tubules, in which only a very occasional cell stained for acid or pepsin. The lamina propria in some specimens contained numerous plasma cells (Fig. 16), but in others showed little infiltration (Fig. 15). These changes represented considerable atrophy of the normal secretory elements of the body of the stomach, and the specimens were grouped as 'gastric atrophy'.

These results are summarized in Table II. They conform in general to the descriptions of gastric histology already published from this Unit (Doig, 1949; Doig and Motteram, 1949–50; Motteram, 1951), but a slightly more detailed classification has been adopted for this larger series.

Serial gastric biopsies in the same patient. A further estimate of the sampling error inherent in blind gastric biopsy was obtained by comparing gastric biopsy specimens obtained from the same patient at different times. This test is in addition to the instances, discussed above, in which two pieces of mucosa were obtained on the same occasion. Gastric biopsy was successfully performed more than once on 161 (25·9 per cent.) of the 623 patients. Thirty-eight of these 161 patients received deep X-ray therapy to the stomach, and these cases are considered separately, leaving 123 patients for present consideration. In 94 (76·4 per cent.) of these instances there was substantial agreement between serial biopsies, while in 29 (23·6 per cent.) there was no such agreement. These figures agree well with the corresponding results when two pieces of mucosa were obtained at the same time. Thus a woman aged 68 years, who

had chronic dyspepsia due to gastritis, underwent gastric biopsy nine times during the years 1948 to 1953. All the biopsy specimens showed both gastritis and atrophy, although the degrees of change varied slightly over the years. A man aged 47 years, who had pernicious anaemia, underwent gastric biopsy on six occasions, and all the specimens were essentially similar in showing gastric atrophy. This case has been reported in detail elsewhere (Finckh and Wood, 1953).

The 29 patients in whom biopsy revealed variations in the history of the gastric mucosa on different occasions require further discussion. Five of these patients had either carcinoma of the stomach or gastric ulcer, and in them the variation in histological appearances was probably due to patchy gastritis about the local lesion. In three patients the changing histological appearances reflected the course of their illness. A man aged 42 years, who had severe ulcerative colitis, underwent gastric biopsy on three occasions; when his symptoms were severe, gastric biopsy twice showed the presence of atrophic gastritis, but a year after colectomy, when his symptoms were much improved, gastric biopsy revealed a normal mucosa. In the remaining 21 patients there was no obvious cause for the variations found on gastric biopsy. In these cases either the gastric lesion was patchy or there were spontaneous variations in the gastric mucosa, but it is not possible to decide between these two possibilities. These patients suffered from various diseases; in nine the final diagnosis was gastritis, three had tertiary syphilis, and three were chronic alcoholics.

Gastritis

There is much disagreement in the medical literature concerning gastritis. Schindler (1947), basing his conclusions on gastroscopic evidence, listed varieties of gastritis, each with a separate clinical picture, but Ricketts, Palmer, and Kirsner (1949) were unable to relate their gastroscopic findings to the symptoms of their patients, and Magnus (1952) in his recent discussion of gastritis almost entirely omits clinical details. This confusion results from several causes. Most clinical studies of gastritis have been without concomitant histological control, the diagnosis being based on clinical grounds alone, on test-meal results (Hurst, 1933), or on gastroscopic findings (Symposium on Symptomatology of Chronic Gastritis, 1943; Schindler, 1947). On the other hand most histological studies of gastritis have been made on material obtained at autopsy (Faber, 1935) or at operation (Magnus, 1952). In the former instance retrospective correlation from autopsy findings is difficult, and does not allow the natural history of the disease to be observed over the years; in the latter instance the clinical features of gastritis *per se* are usually overshadowed or obscured by the coexistence of peptic ulcer or carcinoma.

The first comprehensive study of patients with histological gastritis proved by gastric biopsy was made by Doig and Wood (1952). They found in 112 patients 'a recognizable though variable and usually mild clinical picture' which could be distinguished from that of peptic ulcer. Symptoms of gastritis typically begin in the fifth decade, and are slightly more common in women than in men.

The outstanding symptoms are flatulence and epigastric discomfort; vomiting is sometimes a symptom, but is not usual. The discomfort is rarely described as pain, but commonly as a fullness or a burning sensation, felt diffusely in the epigastrium, and without definite localization or radiation. There is no tender spot such as that usually found with peptic ulcer. The discomfort frequently occurs shortly after meals, and is not relieved by food, but often by alkaline

TABLE III

The Relation between Gastrointestinal Symptoms and Findings on Gastric Biopsy

	Probable basis of gastrointestinal symptoms								
	Gastritis alone		*Gastritis in part*		*Causes other than gastritis*		*No gastro-intestinal symptoms*		
Histological findings	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Total*
Normal	2	*1·2*	8	*4·8*	102	*61·0*	55	*33·0*	167
Slight superficial gastritis	10	*5·6*	1	*0·6*	123	*69·1*	44	*24·7*	178
Moderate or severe superficial gastritis	41	*16·2*	32	*12·6*	101	*40·0*	79	*31·2*	253
Superficial gastritis with atrophy	38	*30·4*	19	*15·2*	26	*20·8*	42	*33·6*	125
Atrophic gastritis	30	*23·5*	25	*19·5*	36	*28·1*	37	*28·9*	128
Severe atrophic gastritis	20	*21·5*	14	*15·1*	15	*16·1*	44	*47·3*	93
Gastric atrophy	11	*19·6*	5	*9·0*	5	*9·0*	35	*62·4*	56
Total	152	*15·2*	104	*10·4*	408	*40·8*	336	*33·6*	1,000

powders. It is periodic, but this is not a conspicuous feature, and both exacerbations and remissions are of short duration. Psychic stress aggravates symptoms in the majority of cases. In most patients there is epigastric tenderness, which is the only abnormal physical sign. When symptoms have been present for long periods, there is evidence of malnutrition: loss of weight, atrophy of the tongue, which may be painful, and angular stomatitis. A moderate degree of iron-deficiency anaemia is frequent, and overt haematemesis may also occur.

In the present series, in order to assess the clinical significance of the various types of gastritis described histologically, the patients were divided into four groups:

1. Patients with gastrointestinal symptoms considered due to gastritis.
2. Patients with gastrointestinal symptoms considered due partly to gastritis and partly to other causes.
3. Patients with gastrointestinal symptoms considered due to causes other than gastritis, such as peptic ulcer, pancreatitis, or hepatitis.
4. Patients without gastrointestinal symptoms.

The correlation between these groups and the histological findings is shown in Table III. The figures show a good correlation; the histological findings, however, were taken into consideration in making the final diagnosis. Of the 167 patients who had a normal mucosa, symptoms were attributed to gastritis in only 10 (6 per cent.); in the remaining 157, gastrointestinal symptoms either could be attributed to other causes or were absent. Similarly, of the patients who had 'slight superficial gastritis' only 11 (6·2 per cent.) had symptoms attributed to gastritis. This figure of about 6 per cent. appears to be a measure of the diagnostic inaccuracy in the series. Because of this similarity

in the diagnosis of patients who had normal mucosae and those who had slight superficial gastritis, and because these slight degrees of change are so frequent, they are not thought to be of any significance, and in the remainder of the present paper these two histological groups are considered together as being within normal limits.

The majority of patients whose symptoms were attributed to gastritis had varying grades of either superficial or atrophic gastritis. In a few the mucosa was normal, and these cases probably represent diagnostic errors. Eleven had gastric atrophy without inflammatory changes: most of these patients had untreated or inadequately treated pernicious anaemia, though a few showed chronic inflammatory gastritis in other biopsy specimens. In 104 instances gastritis was considered to cause some, but not all, of the patient's symptoms. These patients usually had gastritis and some other organic lesion such as pancreatitis, acute hepatitis, or alcoholic cirrhosis; in other cases there was such a pronounced functional element that this was thought to play an important part in the patient's symptoms. The relation between gastritis and functional dyspepsia is still uncertain. Doig and Wood (1952) found that psychic stress aggravated symptoms in their patients who had gastritis, but they considered 'that the most important action of psychic stress is to render that patient sensitive to painful stimuli'. There is, however, considerable evidence that psychic stress and mucosal changes, especially vascularity, are related (Wolff, Wolf, Grace, Holmes, Stevenson, Straub, Goodell, and Seton, 1948; Wretmark, 1953).

In 408 instances the patient had gastrointestinal symptoms which were considered due to causes other than gastritis. The majority (55 per cent.) of these patients had normal mucosae; in many of the others the gastritis was considered to be secondary to lesions such as gastric ulcer or carcinoma, or cholelithiasis with obstructive jaundice. In 336 instances the patient had no gastrointestinal symptoms, although pronounced changes in the gastric mucosa were present in 237 cases (71 per cent.). Many of these patients had gastritis induced by X-ray irradiation, and we have found that this type of gastritis rarely causes symptoms; in other cases the biopsy specimens were obtained from patients receiving treatment for pernicious anaemia. There is, however, no doubt that even in young persons severe gastric changes may be present without symptoms, as in the patient who had atrophic gastritis reported by Doig, Motteram, Weiden, and Wood (1950), and the patient suffering from pernicious anaemia reported by Marmion, Gardner, Saint, and Stubbe (1953), both of whom were in their third decade.

These results suggest that, in the presence of a normal gastric biopsy, one showing only slight superficial gastritis, or one showing complete gastric atrophy without inflammation, it is unlikely that the patient has symptoms due to gastritis. When biopsy reveals other types of gastritis, these may be the cause of symptoms, although this is not usually so; any grade of gastritis may be present without producing symptoms.

X-ray Irradiation of the Gastric Mucosa

Atrophy of the gastric mucosa was purposely produced by X-ray irradiation in the treatment of duodenal ulcer by Bassler (1909), and comprehensive series were later reported by Holman and Lewis (1941) and by Ricketts, Palmer, Kirsner, and Hamann (1948). In 1950 McGeorge in New Zealand introduced radium into the stomach for the same purpose. The histological changes in the gastric mucosa produced by X-ray irradiation were described by Ricketts,

TABLE IV

The Effects of X-ray Irradiation upon the Gastric Mucosa in 159 Gastric Biopsies

	Months after X-ray irradiation																	
Histological result	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*14*	*15*	*18*	*24*	*36*	*Total*
Within normal limits	10	14	3	2	4	5	5	4	1	4	3	..	2	..	..	1	..	..	58
Moderate or severe superficial gastritis	9	16	8	5	7	4	5	..	..	4	..	1	4	1	1	1	3	..	69
Superficial gastritis with atrophy	3	6	1	2	..	..	1	..	..	..	..	..	..	..	..	..	..	..	13
Atrophic gastritis	2	3	2	1	2	1	..	1	..	..	..	..	1	..	..	..	..	1	14
Severe atrophic gastritis	..	1	..	..	1	..	2	1	..	..	..	..	..	..	..	..	..	..	5
Gastric atrophy	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Total	24	40	14	10	14	10	13	6	1	8	3	1	7	1	1	2	3	1	159

Kirsner, Humphreys, and Palmer (1948), who examined sections taken at laparotomy or post-mortem examination. The first comprehensive study of serial gastric biopsies in one patient after X-ray irradiation of the stomach was made by Doig, Funder, and Weiden (1951) in this Unit; they observed atrophy, with a maximum density three weeks after irradiation, followed by slow regeneration of the mucosa. Further reports have been published by Scott, Holman, and Finckh (1953–4) and by Goldgraber, Rubin, Palmer, Dobson, and Massey (1954).

The present series contains 159 biopsies made during, or at varying periods after, X-ray irradiation of the stomach. The irradiation given was a gastric-tissue dose of 1,500r or 2,000r spaced over three weeks (Scott, Holman, and Finckh, 1953–4). In 77 instances the patient was suffering from severe duodenal ulcer, and in 73 others X-ray irradiation was given after antroduodenectomy, in both cases as part of a study of the clinical efficacy of conservative surgery and X-ray irradiation in the treatment of duodenal ulcer (Brown, Scott, Holman, Wood, Finckh, Weiden, and Davis, 1952; Brown and Wood, 1955). The remaining biopsies comprise five performed during the treatment of a retroperitoneal sarcoma with large doses of X-ray irradiation, and four from patients treated by this method for anastomotic ulcer. The histological findings in these cases are shown in Table IV, and agree well with those previously reported (Doig, Funder, and Weiden, 1951; Scott, Holman, and Finckh, 1953–4). There was some variation from patient to patient, but in general the X-ray irradiation produced a moderate superficial gastritis, frequently with some glandular atrophy. The effects were greatest about two or three months after irradiation, but changes were noted within a month of irradiation. There was subsequently a gradual return to normal, and six months after irradiation changes were

slight in the majority of cases. In a few instances moderate superficial or atrophic gastritis persisted for much longer periods: most of these patients had undergone limited gastric resection (antroduodenectomy). There was no evidence to suggest that X-ray irradiation in these doses would produce permanent changes in the gastric mucosa, nor did gastric atrophy develop in any case. The results of histamine test meals closely paralleled the histological changes in these patients. The gastritis produced by X-ray irradiation did not

TABLE V

Classification of Gastric Biopsies according to the Age of the Patient at the time of Biopsy

Patients who received X-ray irradiation of the stomach are excluded

	Age of patient (years)													
	0–20		*21–30*		*31–40*		*41–50*		*51–60*		*61–70*		*71 and over*	
Histological results	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Total*
Within normal limits	7	*77·8*	40	*50·6*	65	*46·3*	68	*38·9*	68	*30·5*	33	*18·6*	5	*13·5*	286
Moderate or severe superficial gastritis	1	*11·1*	23	*29·1*	32	*22·7*	42	*24·0*	42	*18·1*	34	*19·2*	10	*27·1*	184
Superficial gastritis with atrophy	..	..	7	*8·9*	16	*11·3*	25	*14·3*	25	*11·3*	33	*18·6*	6	*16·2*	112
Atrophic gastritis	1	*11·1*	5	*6·3*	16	*11·3*	20	*11·4*	36	*16·2*	30	*17·0*	6	*16·2*	114
Severe atrophic gastritis	..	..	3	*3·8*	8	*5·6*	13	*7·4*	35	*15·7*	23	*13·0*	6	*16·2*	88
Gastric atrophy	..	..	1	*1·3*	2	*2·8*	7	*4·0*	18	*8·2*	24	*13·6*	4	*10·8*	56
Total	9	*100*	79	*100*	139	*100*	175	*100*	224	*100*	177	*100*	37	*100*	840

cause symptoms: the patients had no dyspepsia, and ate normally. This point was also noted by Ricketts, Kirsner, Humphreys, and Palmer (1948). In addition one biopsy specimen was obtained from a female patient aged 26 years who had Hodgkin's disease, after a prolonged course of nitrogen mustard; this specimen showed only slight superficial gastritis.

Results of Gastric Biopsy in Other Conditions

Although each patient has not been studied in full detail, it has been possible from the present series to study the gastric biopsy findings in various conditions other than gastritis. For this purpose patients who received X-ray irradiation of the stomach have been excluded.

Age. The biopsies are classified according to the age of the patient at the time of biopsy in Table V. The results show that, although the frequency of gastritis increases with age, a normal biopsy specimen was found in five of 37 biopsies (13·5 per cent.) from patients aged over 70 years, and conversely two of nine biopsies from patients in the second decade showed significant abnormality. This result is in part due to the difference in the diseases which cause patients of different ages to come up for investigation. Many of the younger patients were either medical students or sufferers from duodenal ulcer, while many of the elderly had gastric carcinoma or pernicious anaemia. It is apparent, however, that neither gastritis nor gastric atrophy is normal in elderly patients, but that they are pathological changes more frequent with advancing years, as are atheroma and prostatic hypertrophy. This increasing

frequency of gastritis with advancing years provides the pathological basis of the known increased frequency of achlorhydria in the aged (Davies and James, 1930–1).

Gastric ulcer. The 65 biopsies from cases of proved gastric ulcer showed a wide range of appearances (Table VI). Twenty-three (35·4 per cent.) were within normal limits; 23 (35·4 per cent.) showed superficial gastritis, with

TABLE VI

The Results of Gastric Biopsy in some Diseases of the Alimentary Tract

Histological results	*Gastric ulcer*		*Duodenal ulcer*		*Other peptic ulcers*	*Prolapsed gastric mucosa*	*Carcinoma of the stomach*	*Other neoplasms*	*Other diseases of the alimentary canal*	*Virus hepatitis*	*Cirrhosis of the liver*		*Pancreatitis*		*Cholelithiasis*
	Number	*%*	*Number*	*%*							*Number*	*%*	*Number*	*%*	
Within normal limits	23	*35·4*	59	*60·2*	11	7	4	4	9	16	19	*47·5*	16	*41·0*	4
Moderate or severe superficial gastritis	13	*20·0*	29	*29·6*	8	..	6	2	5	4	10	*25·0*	8	*20·5*	4
Superficial gastritis with atrophy	10	*15·4*	5	*5·1*	..	..	4	3	..	..	4	*10·0*	1	*2·6*	3
Atrophic gastritis	12	*18·4*	5	*5·1*	2	1	4	..	2	1	3	*7·5*	10	*25·6*	4
Severe atrophic gastritis	7	*10·8*	..	..	1	..	1	3	2	..	2	*5·0*	2	*5·1*	3
Gastric atrophy	..	..	..	..	..	..	1	1	..	1	2	*5·0*	2	*5·1*	..
Total	65	*100*	98	*100*	22	8	20	13	18	22	40	*100*	39	*100*	18

tubular atrophy in 10 (15·4 per cent.); 19 (29·2 per cent.) showed atrophic gastritis, which was severe in seven (10·8 per cent.). The high incidence of gastritis conforms generally with the incidence of gastritis recorded in specimens obtained during gastric resection for gastric ulcer (Puhl, 1927; Magnus, 1952). It is considered to be due to an inflammatory reaction which spreads from the ulcer site. We have termed this condition 'zonal gastritis'. Histologically it is indistinguishable from other types of gastritis, the precise histological findings depending on the distance between the ulcer crater and the site of biopsy. No evidence has been obtained that gastritis predisposes to gastric ulcer: a follow-up for at least five years of patients who had atrophic gastritis proved by biopsy has revealed only one case of peptic ulcer (Fairley, Mackay, Turner, and Joske, 1955).

Duodenal ulcer. In contrast with the results found in gastric ulcer, 59 (60·2 per cent.) of the biopsy specimens from patients with duodenal ulcer were within normal limits, 34 (34·7 per cent.) showed superficial gastritis, and only five (5·1 per cent.) atrophic gastritis (Table VI). These histological findings reflect the known contrast between the large over-secreting stomach in cases of duodenal ulcer and the small stomach, with reduced secretion, in cases of gastric ulcer (Cox, 1952). In specimens taken at operation from patients with duodenal ulcer Magnus (1952) found that gastritis was mild and localized to the antrum in all cases, although Puhl (1927) found erosive gastritis as frequently associated with duodenal as with gastric ulcer.

Other forms of peptic ulcer. Three biopsies were obtained from patients with

coexistent gastric and duodenal ulcer, and six from patients with anastomotic ulcer. The results were consistent with the presence of a zonal gastritis in some cases (Table VI). Two patients were shown at laparotomy to have 'acute gastric erosion'; biopsy showed a normal mucosa in one and moderate superficial gastritis in the other. Six patients had haematemesis, and five had had recent severe ulcer dyspepsia, without gastroscopic or radiological evidence of peptic ulcer. In five of these patients a presumptive diagnosis of acute peptic ulcer was made when a normal mucosa was shown by biopsy. The other six had significant degrees of gastritis, and in them the diagnosis between gastritis and acute peptic ulcer is unresolved.

Prolapsed gastric mucosa. Eight biopsies were obtained from patients in whom prolapse of the gastric mucosa through the pylorus had produced symptoms (Johnson, 1952). Seven of these specimens were within normal limits, and one showed atrophic gastritis (Table VI). These results do not accord with the theory that this condition results from chronic gastritis (Eliason, Pendergrass, and Wright, 1926), although antral gastritis has not been excluded.

Carcinoma of the stomach. Of 20 biopsies obtained from patients with proved carcinoma of the stomach only four were within normal limits, and the remainder showed all degrees of gastritis up to complete gastric atrophy (Table VI). These findings are probably largely a result of zonal gastritis, for a five-year follow-up of patients with proved gastritis has yielded no case in which carcinoma supervened, and the incidence of gastritis associated with malignant disease of other organs is also high (Table VI). Although it has been strongly urged that gastritis is a precancerous lesion (Hurst, 1929), our experience with gastric biopsy does not support this contention. As regards the gastric atrophy of pernicious anaemia, the association of pernicious anaemia and carcinoma is still *sub judice* (Wilkinson, 1933; Mosbech and Videbaek, 1950; Rigler, Kaplan, and Fink, 1945).

Other diseases of the alimentary tract. The numbers of biopsies in such cases were too few to allow conclusions to be drawn. It is of interest that two of 10 biopsies obtained from cases of ulcerative colitis showed atrophic gastritis, and in three patients with the malabsorption syndrome changes were very slight.

Acute virus hepatitis. Twenty-two biopsies were obtained from patients with virus hepatitis, which was acute in 15 and chronic in seven instances. Changes were slight: four biopsies showed significant superficial gastritis, one atrophic gastritis, and one gastric atrophy (Table VI). One of these patients was also a chronic alcoholic. The patient who had gastric atrophy provided no evidence of either pernicious anaemia or subacute combined degeneration of the cord. These results do not support the contention that associated gastritis is a cause of symptoms in acute virus hepatitis (Knight and Cogswell, 1945; Loughead and Golding, 1952).

Cirrhosis of the liver. The 40 biopsies from patients with established cirrhosis of the liver (excluding haemochromatosis) showed abnormality in 21 cases (Table VI). The majority of these patients were chronic alcoholics or had chronic malnutrition; seven had chronic virus hepatitis, one syphilis, and one

chronic brucellosis. The aetiology was unknown in eight. The incidence of gastritis was less in cirrhosis due to chronic virus hepatitis; only one of these seven biopsies showed significant changes.

Pancreatitis. Gastritis is apparently very frequent in pancreatitis; some tubular atrophy was present in 15 of 39 biopsies (38·6 per cent.), and two showed complete gastric atrophy (Table VI).

TABLE VII

The Results of Gastric Biopsy in Pernicious Anaemia, Subacute Combined Degeneration of the Cord, and some Diseases not primarily involving the Alimentary Tract

Histological result	*Pernicious anaemia and subacute combined degeneration of the cord*	*Other anaemias*	*Other neuropathies*	*Haemochromatosis and haemosiderosis*	*Syphilis*	*Sjögren's disease*	*Diabetes mellitus*	*Thyrotoxicosis*
Within normal limits	..	4	23	9	1	..	8	4
Moderate or severe superficial gastritis	..	5	10	5	6	1	4	1
Superficial gastritis with atrophy	9	4	9	3	2	3	5	2
Atrophic gastritis	16	5	6	..	7	1	3	..
Severe atrophic gastritis	35	4	1	1	4	..	..	1
Gastric atrophy	40	..	..	..	1	..	..	..
Total	100	22	49	18	21	5	20	8

Cholelithiasis. The biopsies from 18 patients whose symptoms were attributed to cholelithiasis showed a high incidence of gastritis; only four were normal (Table VI). Some degree of atrophy was seen in 10. It is possible that associated gastritis is a cause of the flatulent dyspepsia which is so common in cholelithiasis and closely resembles the dyspepsia of gastritis (Doig and Wood, 1952).

Pernicious anaemia and subacute combined degeneration of the cord. The frequent, if not invariable, occurence of achlorhydria in pernicious anaemia has been known for many years (Fenwick, 1870). Much attention has been paid to the nature of the gastric lesion causing this achlorhydria, and this work has recently been fully reviewed by Molofsky and Hollander (1951). It is based largely upon gastroscopic studies; relatively few histological reports (based on autopsy material) have been published. In the present series 100 biopsies were performed in cases of pernicious anaemia or subacute combined degeneration of the cord, or both. The results are shown in Table VII. The figures are striking; all the specimens showed severe gastric changes, atrophic gastritis or gastric atrophy being present in 91 of them. The other nine biopsies showed severe superficial gastritis with atrophy, and in three of these patients subsequent biopsies demonstrated atrophic gastritis. All these patients had histamine-fast achlorhydria. Other reports of gastric biopsy in pernicious anaemia and subacute combined degeneration of the cord have been published in recent years

from this Unit and elsewhere. All agree with the present invariable finding of severe gastric changes, frequently gastric atrophy (Doig, 1949; Doig and Wood, 1950; Doig and Motteram, 1949–50; Doig, Motteram, Robertson, and Wood, 1950; Motteram, 1951; Wood, 1951; Finckh and Wood, 1953; Badenoch and Richards, 1953; Doig, 1954; Badenoch, 1954). These changes are in no way affected by adequate treatment with liver extracts or vitamin B_{12}, and probably antedate the presence of either haematological or neurological abnormality. Thus a man of 65 years was shown in 1949 by gastric biopsy to have complete gastric atrophy and achlorhydria, without symptoms or other clinical or laboratory signs, but in 1954 he developed macrocytic anaemia and subacute combined degeneration of the cord, which responded to treatment with vitamin B_{12}. Further gastric biopsies still showed complete gastric atrophy. This case will be reported fully elsewhere (Robertson, Wood, and Joske, 1955). In pernicious anaemia and subacute combined degeneration of the cord gastric biopsy will thus demonstrate gross abnormality in the gastric mucosa in all cases, even after adequate treatment. This is of very great diagnostic value in doubtful cases, or where treatment has been given without adequate prior investigation (Doig, Motteram, Robertson, and Wood, 1950). In 16 biopsies gastric atrophy was found with no evidence of pernicious anaemia. In one case (described above) macrocytic anaemia has developed subsequently. Three of the other biopsies were from patients who at other times showed atrophic gastritis, and the remainder were from patients with a variety of clinical conditions (see Tables III and VI).

Other types of anaemia. Twenty-two biopsies were obtained from patients who had other types of anaemia (excluding overt haemorrhage), and the results are summarized in Table VII. Eleven patients had hypochromic microcytic anaemia (Witts, 1932); in six biopsy showed atrophic gastritis, and in three superficial gastritis, while in two the appearances were within normal limits. These results suggest that the achlorhydria so frequent in this type of anaemia results from inflammatory gastritis (Hurst, 1932; Oliver and Wilkinson, 1933). Seven biopsies from patients with macrocytic anaemia due to causes other than pernicious anaemia showed a normal mucosa in two, superficial gastritis in three, and atrophic gastritis in two cases.

Other neuropathies. The biopsy findings in subacute combined degeneration of the cord contrast with those seen in other neuropathies liable to present difficulty in diagnosis. Of 49 biopsies, 31 were from cases of chronic alcoholism with neuritis or encephalopathy, and the remainder from patients with peripheral neuritis from other causes, such as diabetes mellitus or malnutrition. The results (Table VII) show that 23 biopsy specimens were within normal limits, 19 showed superficial gastritis, and only seven showed atrophic gastritis. No biopsy showed gastric atrophy. These results emphasize the diagnostic value of gastric biopsy in pernicious anaemia and subacute combined degeneration of the cord.

Haemochromatosis and haemosiderosis. Fifteen biopsies from patients who had haemochromatosis showed little abnormality, six showing superficial gas-

tritis. The presence of haemosiderin does not therefore necessarily result in gastritis (Althausen, Doig, Weiden, Motteram, Turner, and Moore, 1951). In contrast, three biopsies from patients with transfusion siderosis (two from the case of red-cell aplasia reported by Cowling and Schwarz, 1952) all showed gastritis with some tubular atrophy.

Syphilis. The 21 biopsies from patients with tertiary syphilis show a remarkably high incidence of gastritis; only one specimen was within normal limits

TABLE VIII

The Effects of Nutritional Status and Chronic Alcoholism on the Gastric Biopsy Findings

	Chronic alcoholism		*Nutrition*								*Hypo-proteinaemia*	
	Good				*Fair*		*Poor*		*Bad*			
Histological findings	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Within normal limits	44	*47*	74	*36·8*	58	*36·0*	57	*29·9*	56	*38·9*	37	*39*
Moderate and severe superficial gastritis	26	*27*	41	*20·4*	37	*23·0*	45	*23·5*	34	*24·5*	22	*23*
Superficial gastritis with atrophy	13	*14*	21	*10·4*	28	*17·4*	28	*14·7*	14	*9·9*	12	*12·5*
Atrophic gastritis	7	*7*	27	*13·4*	15	*9·3*	28	*14·7*	23	*16·2*	10	*10·5*
Severe atrophic gastritis	4	*4*	21	*10·4*	14	*8·7*	26	*13·6*	9	*6·3*	8	*8·5*
Gastric atrophy	1	*1*	17	*8·5*	9	*5·6*	7	*3·6*	6	*4·2*	6	*6·5*
Total	95	*100*	201	*100*	161	*100*	191	*100*	142	*100*	95	*100*

(Table VII). The histological appearances did not differ from those seen in non-syphilitic patients, and it is impossible to say whether these patients had in fact syphilitic gastritis or, more probably, chronic gastritis and syphilis. The diagnosis of syphilitic gastritis is notoriously difficult (Singer, 1933; Boyd, 1944).

Other conditions. Since significant gastritis was present in all five biopsy specimens from patients with Sjögren's syndrome (Table VII), and achlorhydria has been reported as occurring in this condition (Weber, 1945; Cadman and Robertson, 1952), it is possible that the gastric mucosa shares in the inflammatory atrophy found elsewhere. Of the other conditions included in the present series, the frequency of gastritis in diabetes mellitus and thyrotoxicosis is noteworthy (Table VII). In five of the patients with thyroid disease attempted autoradiography of the biopsy material with ^{131}I was unsuccessful.

Nutritional status. In 695 of the 840 instances in which gastric biopsy was performed in the absence of X-ray irradiation of the stomach, it was possible to make a reasonable assessment of the patient's nutritional status based on the history, examination, and dietetic history. On this basis four grades of nutritional status, good, fair, poor, and bad, have been distinguished, and the results of biopsy are related to them in Table VIII. There is no increase in the frequency or severity of the gastric changes with increasingly poor nutrition; this fact suggests that malnutrition alone is not a cause of gastritis. A similar conclusion follows from an analysis of 95 biopsies from patients with hypoproteinaemia (total serum-protein less than 6·0 gm. per 100 ml.), which also shows no increased frequency of gastritis.

Chronic alcoholism. Fifty-one of 95 biopsies showed significant changes (Table VIII), reflecting the high incidence of gastrointestinal disease in alcoholic

subjects (Joske and Turner, 1952; Isbister, 1954). The changes were not generally gross: 39 showed superficial gastritis, 11 atrophic gastritis, and one gastric atrophy without pernicious anaemia. An earlier study of gastric biopsy in alcoholism (Finckh, Dale, Joske, and Saint, 1952) showed similar results, although Cox (1948) did not consider that alcoholism caused gastritis. Since we believe that malnutrition does not cause gastritis, the changes observed may represent direct toxic effects of ethyl alcohol.

TABLE IX

Results of Gastric Biopsy in Other Conditions

Histological findings	*Previous gastric surgery*	*Pyloric obstruction*	*Haematemesis and melaena*	*Occult blood in faeces*	*Previous antibiotic therapy*
Within normal limits	14	12	22	17	16
Moderate or severe superficial gastritis	15	14	6	15	15
Superficial gastritis with atrophy	4	2	4	6	2
Atrophic gastritis	6	4	3	5	10
Severe atrophic gastritis	4	1	5	8	12
Gastric atrophy	1	..	..	2	3
Total	44	33	40	53	58

Previous gastric surgery. The 44 biopsies performed after previous gastric resection or gastroenterostomy show a high incidence of gastritis (Table IX), as was also noted by Palmer (1953). The lapse of time between surgery and biopsy did not influence the incidence of gastritis. The condition seen in these cases is a type of zonal gastritis, which is greatest about the anastomosis or stoma; we have termed it 'gastric stomatitis'. In our experience gastric stomatitis is often a cause of symptoms after gastric surgery, but one that is rarely recognized.

Pyloric obstruction. Thirty-three biopsies were done in cases of organic pyloric stenosis due, in the majority of cases, to duodenal ulcer. They show a high incidence of gastritis (Table IX).

Gastrointestinal haemorrhage. In 40 instances biopsy was performed within one month of previous haematemesis or melaena, or both, in patients in whom no evidence of peptic ulcer or neoplasm was obtained (Table IX). In 22 cases the specimens were within normal limits; the remaining 18 showed various grades of gastritis. Although some of these results may be due to zonal gastritis about an undetected acute gastric ulcer, it is considered that in some patients gastritis may lead to gastrointestinal haemorrhage without an established peptic ulcer. Similar conclusions were reached from the gastric biopsy findings in patients who had occult blood in the faeces in the absence of any obvious anatomical cause, cases of frank haematemesis or melaena being excluded. There were 53 such cases, and the majority showed varying degrees of gastritis up to complete gastric atrophy; only 17 were within normal limits (Table IX). There is little doubt that gastritis must be considered as one cause of occult blood in the faeces.

Effect of antibiotics. Various antibiotics, singly or in combination, were

administered in therapeutic doses before biopsy in 58 instances, and no significant beneficial effects were demonstrated (Table IX). In 24 of the 58 cases previous biopsy specimens, taken before therapy, were available for comparison, and it was considered that there was histological improvement in seven, deterioration in nine, and no change in eight cases. The incidence of gastritis in these biopsies is high because patients with gastritis were selected for therapy.

TABLE X

Relation of Gastric Biopsy Findings to Volume and Acidity of Fasting Gastric Contents

	Fasting gastric contents											
			No free HCl present				*Free HCl present*					
	Nil		*Volume < 10 ml.*		*Volume > 10 ml.*		*Volume < 10 ml.*		*Volume > 10 ml.*		*Total*	
Histological findings	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Within normal limits	12	*4·2*	49	*17·0*	35	*12·2*	47	*16·3*	145	*50·3*	288	*100*
Moderate or severe superficial gastritis	9	*4·1*	68	*31·5*	73	*33·8*	14	*6·5*	52	*24·1*	216	*100*
Superficial gastritis with atrophy	9	*9·2*	32	*33·0*	31	*32·0*	13	*13·4*	12	*12·4*	97	*100*
Atrophic gastritis	9	*8·4*	45	*42·1*	38	*35·5*	3	*2·8*	12	*11·2*	107	*100*
Severe atrophic gastritis	20	*23·3*	50	*58·1*	11	*12·8*	2	*2·3*	3	*3·5*	86	*100*
Gastric atrophy	10	*24·4*	26	*63·4*	5	*12·2*	..	..	..	..	41	*100*
Total	69	*8·3*	270	*32·4*	193	*23·1*	79	*9·5*	224	*26·7*	835	*100*

Relation of Gastric Biopsy to Other Gastric Investigations

Fasting gastric residue. Aspiration of the stomach before gastric biopsy provided an opportunity to relate the histological appearances of the gastric mucosa to the fasting gastric contents. The volume and presence or absence of free hydrochloric acid (determined by immediate addition of Töpfer's reagent) were known in 835 of the 1,000 cases of biopsy, and are shown with the corresponding biopsy findings in Table X. Patients receiving X-ray irradiation are included in these figures. There is clearly a general correlation between the histological findings and the fasting gastric residue. Thus, of the 288 instances in which the biopsy findings were within normal limits, free hydrochloric acid was present in 192 (66·7 per cent.); at the other extreme, of 41 cases of gastric atrophy, none showed free hydrochloric acid in the fasting gastric contents, and in 36 instances (87·8 per cent.) the volume obtained was less than 10 ml. The volume and acidity of the fasting gastric contents thus reflect changes in the gastric mucosa, and are a guide to their presence, as has been suggested by Bloomfield, Chen, and French (1940).

Histamine test meal. The relation between histological findings and the gastric secretions shown by the fasting gastric contents is confirmed by the correlation between histological findings and the results of standard histamine test meals. In 784 of the 1,000 cases a histamine test meal was performed within two weeks of gastric biopsy, and the results obtained are shown in Table XI. Patients who received X-ray irradiation are included in these figures. On 352 occasions estimations of pepsin secretion, by the method of Anson and Mirsky (1932–3), were made simultaneously with the histamine test meals, and the results are correlated with the biopsy findings in Table XII. These results show good

agreement between the biochemical and histological findings, especially as regards the secretion of acid; in our experience the histamine test meal is a useful test of gastric function, and gives a good indication of histological changes in the stomach. The results previously reported from this Unit by Wood, Doig, Motteram, Weiden, and Moore (1949) and by Funder and Weiden (1952) are confirmed. Achlorhydria is thus rare in the absence of significant

TABLE XI

Relation between Results of Gastric Biopsy and Acid Secretion after Histamine Test Meal

	Acid secretion after 0·3 mg. histamine (N/10 HCl %)									
	Nil		*1–20*		*21–60*		*61 and over*		*Total*	
Histological findings	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Within normal limits	37	*13·5*	29	*10·5*	114	*41·5*	95	*34·5*	275	*100*
Moderate or severe superficial gastritis	51	*24·3*	55	*26·2*	74	*35·2*	30	*14·3*	210	*100*
Superficial gastritis with atrophy	50	*58·1*	20	*23·3*	10	*11·6*	6	*7·0*	86	*100*
Atrophic gastritis	71	*71·0*	13	*13·0*	11	*11·0*	5	*5·0*	100	*100*
Severe atrophic gastritis	52	*72·2*	10	*13·9*	7	*9·7*	3	*4·2*	72	*100*
Gastric atrophy	39	*95·1*	2	*4·9*	..	..	..	..	41	*100*
Total	300	*38·2*	129	*16·5*	216	*27·6*	139	*17·7*	784	*100*

TABLE XII

Relation between Results of Gastric Biopsy and Pepsin Secretion after 0·3 mg. Histamine

	Pepsin Secretion							
	<40 units		*41–60 units*		*>60 units*		*Total*	
Histological Findings	*Number*	*%*	*Number*	*%*	*Number*	*%*	*Number*	*%*
Within normal limits	37	*37·8*	15	*15·3*	46	*46·9*	98	*100*
Moderate or severe superficial gastritis	52	*47·7*	15	*13·8*	42	*38·5*	109	*100*
Superficial gastritis with atrophy	26	*61·9*	7	*16·7*	9	*21·4*	42	*100*
Atrophic gastritis	43	*79·8*	3	*5·5*	8	*14·7*	54	*100*
Severe atrophic gastritis	25	*83·3*	2	*6·7*	3	*10·0*	30	*100*
Gastric atrophy	17	*89·4*	1	*5·3*	1	*5·3*	19	*100*
Total	200	*56·8*	43	*12·2*	109	*31·0*	352	*100*

change in the gastric mucosa, which was present in 263 of 300 instances (87·7 per cent.) in which the histamine test meal revealed achlorhydria. Achlorhydria was, however, found in 37 instances in which the biopsy findings were within normal limits. These patients varied in age from 20 to 65 years. Some were receiving X-ray irradiation to the stomach at the time of biopsy, and in some others biopsy was taken after acute alcoholic excess. In the majority no explanation was apparent, and many had a normal secretion of acid at subsequent tests.

Barium meal. A barium meal examination was performed within two weeks of gastric biopsy in 314 of the 840 instances in which biopsy was performed on patients who did not receive X-ray irradiation of the stomach. The corresponding radiological and histological results are shown in Table XIII. No relation between them is apparent. Although many radiological signs of gastritis have been described (Kinsella, 1954), the evidence suggests that radiological examination of the stomach is of the greatest aid in the diagnosis of focal lesions, such

TABLE XIII

The Radiological and Histological Diagnosis in 314 Patients subjected to Gastric Biopsy

	Histological diagnosis						
Radiological diagnosis	*Within normal limits*	*Moderate or severe superficial gastritis*	*Superficial gastritis with atrophy*	*Atrophic gastritis*	*Severe atrophic gastritis*	*Gastric atrophy*	*Total*
No abnormality detected	68	27	25	23	18	16	177
Duodenal ulcer	32	20	5	2	..	..	59
Gastric ulcer	13	9	10	7	3	..	42
Duodenal ulcer and gastric ulcer	1	..	1	..	..	..	2
Carcinoma of stomach	3	5	3	2	2	..	15
Duodenal diverticulum or polyp	3	1	..	1	1	..	6
Partial gastrectomy or gastro-enterostomy	1	2	..	2	..	..	5
Hypertrophic gastritis	2	1	..	..	..	..	3
Prolapsed gastric mucosa	1	..	..	..	1	..	2
Hiatus hernia	1	1	..	..	..	..	2
Small-bowel disturbance	..	..	..	..	1	..	1
Totals	125	66	44	37	26	16	314

as peptic ulcer and carcinoma, but of little aid in the diagnosis of gastritis, since there is no correlation between the radiological and histological findings. Blind gastric biopsy, on the other hand, gives valuable help in the diagnosis of diffuse gastric lesions, but little help in the diagnosis of focal lesions. Gastric biopsy and barium meal examination are thus complementary, and both are required for the complete diagnosis of gastric disease. In three instances the radiologist reported the presence of 'hypertrophic gastritis'; in two of these the biopsy specimen was normal, and the third showed moderate superficial gastritis. We have not yet obtained a gastric biopsy showing so-called hypertrophic gastritis, and doubt whether it is a histological entity.

Gastroscopy. There is great divergence of written opinion concerning the gastroscopic diagnosis of gastritis and gastric atrophy. Some authors (Ricketts, Palmer, and Kirsner, 1949) have been unable to relate gastroscopic appearances to symptoms, while others (Schindler, 1947) have distinguished varieties of gastritis, each with a separate clinical picture, based upon gastroscopic diagnosis. The controversy concerning possible regeneration of the gastric mucosa in adequately treated pernicious anaemia also stems from attempts to interpret

gastric histology from gastroscopic findings (Jones, Benedict, and Hampton, 1935; Schindler and Serby, 1939; Molofsky and Hollander, 1951; Finckh and Wood, 1953). In the present series gastroscopy was performed at the same time as, or within two weeks of, gastric biopsy in 258 instances, and the gastroscopic and histological findings in these instances are shown in Table XIV. The results show that in our hands there has been little correlation between gastroscopic appearances and histological findings. Of the 164 instances in which

TABLE XIV

The Relation between the Gastroscopic and Histological Diagnosis in 258 Patients subjected to Gastric Biopsy

	Histological diagnosis						
Gastroscopic diagnosis	*Within normal limits*	*Moderate or severe superficial gastritis*	*Superficial gastritis with atrophy*	*Atrophic gastritis*	*Severe atrophic gastritis*	*Gastric atrophy*	*Total*
No abnormality detected	87	39	17	10	6	5	164
Gastritis or gastric atrophy	10	7	8	7	5	6	43
Gastric ulcer	12	6	4	4	3	..	29
Carcinoma of stomach	..	2	3	2	2	..	9
After operation:							
No abnormality detected	..	3	..	1	1	..	12
Gastric stomatitis	1	2	..	1	..	..	
Other diagnoses	1	1	..	1	..	..	
Pyloric stenosis	1	..	..	..	..	..	1
Totals	112	60	32	26	17	11	258

gastroscopy was reported to show no abnormality, a significant degree of gastritis was present in 77, while 21 showed atrophic gastritis or gastric atrophy. On the other hand, in the 43 cases in which gastroscopy was reported to show either gastritis or gastric atrophy, all degrees of histological appearance occurred, from a normal mucosa to severe atrophic gastritis and gastric atrophy. For these reasons we feel that the major diagnostic use of gastroscopy is in the detection of focal rather than of diffuse inflammatory or atrophic changes, and that the latter are more efficiently diagnosed by gastric biopsy. In this respect gastroscopy and gastric biopsy are complementary, as are radiology and gastric biopsy.

Conclusion

It is apparent from these results that gastric biopsy by the present technique is a safe and efficient method of obtaining specimens of gastric mucosa for histological examination, and that the sampling error inherent in 'blind' gastric biopsy is less than has been suggested. The clinical importance of gastric biopsy in the macrocytic anaemias has already been stressed, but the value of gastric biopsy in the diagnosis of gastritis is not generally appreciated. Much confusion has sprung from attempts to interpret gastroscopic and radiological findings

in histological terms. Our experience suggests that as yet such correlation is not possible, and the diagnosis of gastritis can be made only by gastric biopsy. Nevertheless a definite though variable clinical picture, frequently with histamine-fast achlorhydria, is present in many cases of histological gastritis, although it varies greatly from time to time and from patient to patient. In many cases severe gastritis is present without symptoms. In all these respects gastritis follows the pattern of peptic ulcer, which is characterized by spontaneous exacerbations and remissions. The aetiological factors in the different types of gastritis are ill understood in most cases. The gastritis present in alcoholism, and possibly that found in syphilis, may be tentatively ascribed to these causes, and the changes which follow X-ray irradiation follow a definite pattern. The gastritis associated with focal gastric lesions ('zonal gastritis') is in our opinion usually secondary to the breach of mucosa, although this is not proved. In the majority of cases the aetiology of gastritis is unknown. Although they have been grouped in this report, the histological changes observed form a continuous gradation from the normal, through superficial and atrophic gastritis, to gastric atrophy. This does not necessarily imply that such a progression occurs in each patient, but it means that gastric atrophy is not an entirely specific change in the mucosa exclusive to pernicious anaemia. When repeated biopsies have been made in cases of pernicious anaemia, some patients have always shown complete gastric atrophy, while others have shown atrophic gastritis at some time and gastric atrophy at others. Gastric atrophy may thus result from two different sets of circumstances, being in some cases a genetically determined anomaly of the stomach and in others the end-result of progressive gastritis. This hypothesis, if true, might throw light upon the complex genetic basis of pernicious anaemia. It is apparent that the use of gastric biopsy in clinical research and practice is only beginning, but the results of its use so far suggest that it will be a method of the greatest use in the diagnosis and study of diseases of the stomach.

Acknowledgements

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Summary

1. A study has been made of 1,000 consecutive gastric biopsies in which the histological and clinical material was available for review. The biopsies were obtained by the flexible gastric biopsy tube.

2. The only complication of gastric biopsy observed was haemorrhage, which occurred in 0·8 per cent. of attempted or successful biopsies, and required transfusion in two instances (0·16 per cent.).

3. Failure to obtain adequate histological material at present occurs in about 5 per cent. of attempted biopsies.

4. The histological findings form a continuous gradation from a normal appearance to complete gastric atrophy, but have been grouped into the following categories: normal, superficial gastritis without and with tubular atrophy, atrophic gastritis, severe atrophic gastritis, and gastric atrophy.

5. When serial gastric biopsies were performed upon the same patient, or when two specimens of mucosa were obtained at the same time, agreement between the different samples from one patient was found in about 75 per cent. of cases.

6. 'Gastritis' is considered to be a definite clinical and histological entity, but superficial gastritis and gastric atrophy rarely cause symptoms, while any degree of histological gastritis may be present without symptoms.

7. X-ray irradiation of the gastric mucosa causes pronounced histological changes, usually followed by a return to normal.

8. Gastritis may occur at any age, but is more frequent in the elderly.

9. Where a focal lesion of the stomach is present, a 'zonal gastritis' spreads out from this focus, and is histologically indistinguishable from gastritis due to other causes.

10. Gastritis is frequently associated with pancreatitis, cholelithiasis, chronic alcoholism, syphilis, and the hypochromic anaemia described by Witts (1932). It is infrequent in virus hepatitis. Gross gastric change was present in all of 100 cases of Addisonian pernicious anaemia. There was no apparent relation between nutritional status and gastritis.

11. The fasting gastric residue and results of histamine test meals correlate well with the histology of the gastric mucosa. No correlation has been found between histological and gastroscopic or radiological findings; these are supplementary to gastric biopsy.

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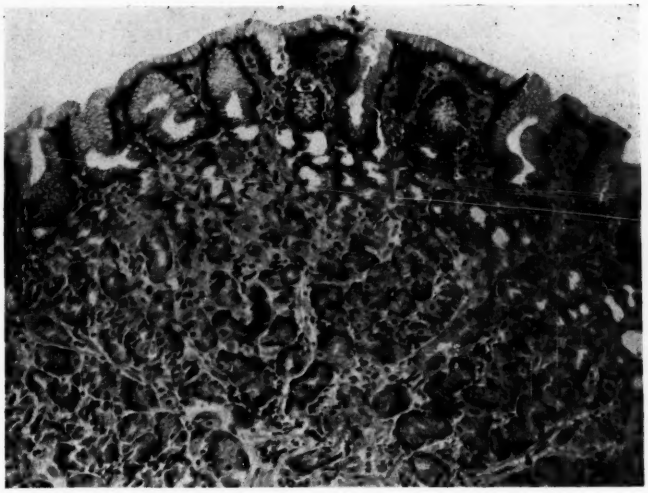

FIG. 1. Normal mucosa from the body of the stomach, obtained by means of a flexible gastric biopsy tube. The surface epithelium is composed of regular columnar cells; the gastric pits are short and lead to regular glands, which are almost entirely composed of acid- and pepsin-secreting cells. The substantia propria of the mucosa contains only an occasional lymphocyte or plasma cell, and a few fine strands of plain muscle run upwards through the mucosa from the muscularis (haematoxylin and eosin, $\times 150$)

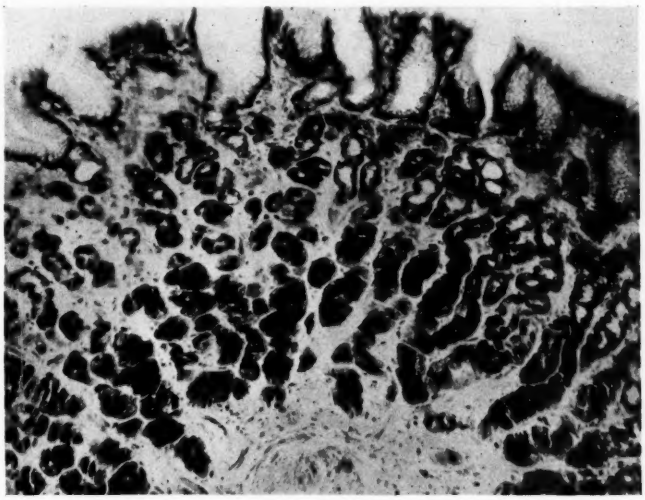

FIG. 2. Normal mucosa. The same portion of mucosa stained to show the acid-secreting cells (light) and pepsin-secreting cells (dark) of the tubules. With this stain the actual colours of these cells are pink to red and violet respectively, while non-specific tubular cells stain a pale greenish brown (trichrome, $\times 150$)

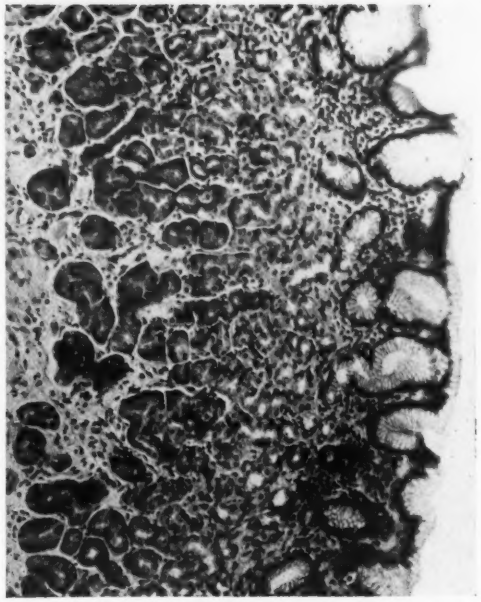

FIG. 3. Slight superficial gastritis. The mucosa shows slight infiltration of the superficial portions of the substantia propria with lymphocytes and plasma cells. This amount of infiltration is taken to be just above normal limits. The mucosa is of normal width, and the tubules are composed of normal acid- and pepsin-secreting cells (see Fig. 4) (haematoxylin and eosin, $\times 150$)

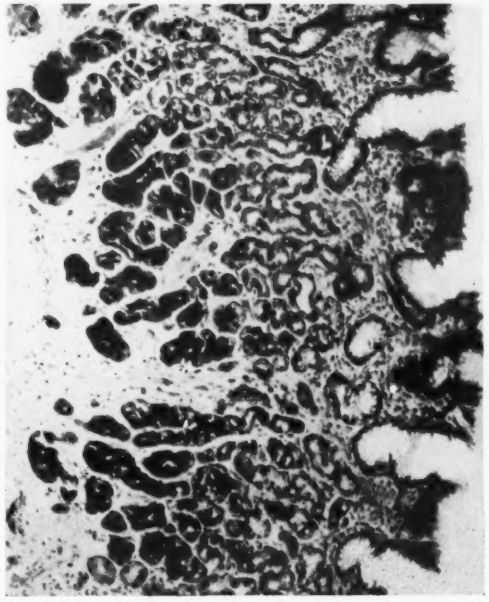

FIG. 4. Slight superficial gastritis. The same specimen as Fig. 3, stained to show the acid- and pepsin-secreting cells. These are present in the tubules in normal numbers. The slight superficial inflammatory infiltration can also be seen with this stain (trichrome, $\times 150$)

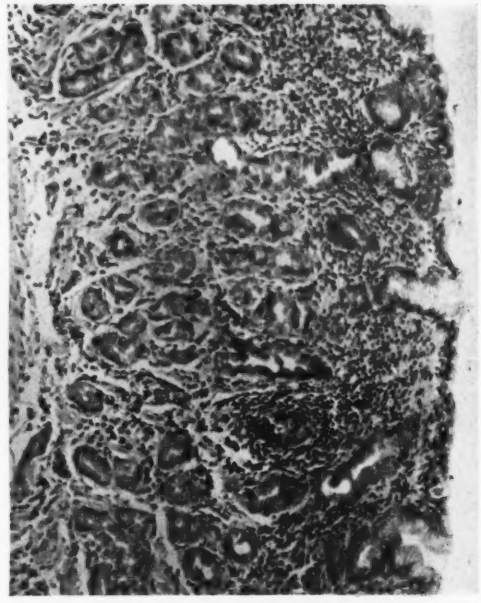

FIG. 5. Severe superficial gastritis. The surface epithelium is partly flattened and irregular, but the gastric pits and tubules are of normal structure. There is considerable infiltration of the upper half of the substantia propria with plasma cells and lymphocytes, and in some areas with groups of polymorphs (haematoxylin and eosin, $\times 150$)

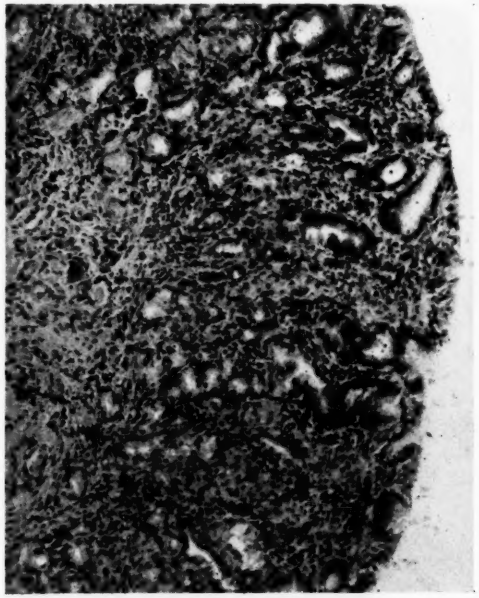

FIG. 6. Moderately severe gastritis with slight atrophy. The surface epithelium is slightly irregular, and the pits lead to tubules which are slightly tortuous and slightly reduced in amount. There is diffuse infiltration with plasma cells, lymphocytes, and polymorphs throughout the substantia propria and extending downwards into the muscularis (haematoxylin and eosin, ×150)

FIG. 7. Severe gastritis with considerable atrophy ('atrophic gastritis'). The surface epithelium is slightly irregular. The pits are slightly elongated and lead to tubules which are considerably reduced in amount. The substantia propria is heavily infiltrated with plasma cells, polymorphs, and lymphocytes, and this infiltration extends into the muscularis. Groups of polymorphs enmeshed in mucus are seen in several of the pits (haematoxylin and eosin, ×150)

FIG. 8. Severe gastritis with considerable atrophy ('atrophic gastritis'). The changes here appear slightly more chronic than those in Fig. 7. Although the amount of atrophy appears the same and the infiltration appears as extensive and heavy, the surface epithelium is regular, and the infiltrating inflammatory cells are almost entirely plasma cells (haematoxylin and eosin, ×150)

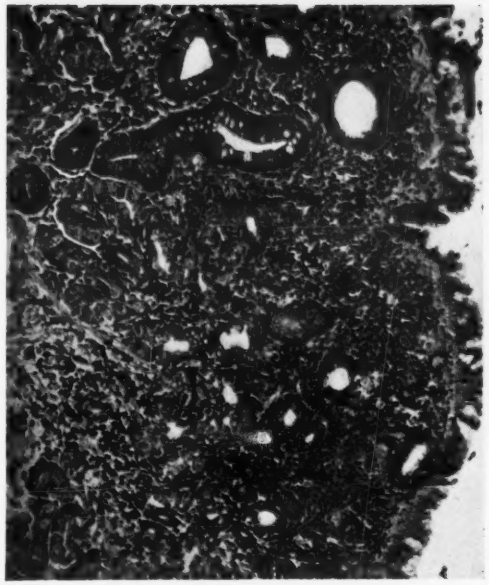

FIG. 9. Severe gastritis with considerable atrophy ('atrophic gastritis'). In this specimen the surface epithelium is slightly irregular and the tubules are tortuous and considerably reduced in amount. Several pits in the upper part of the picture are dilated, elongated, and partly composed of goblet cells which stain deeply with mucicarmine. There is considerable infiltration of the substantia propria with plasma cells, lymphocytes, and groups of polymorphs (haematoxylin and eosin, ×150)

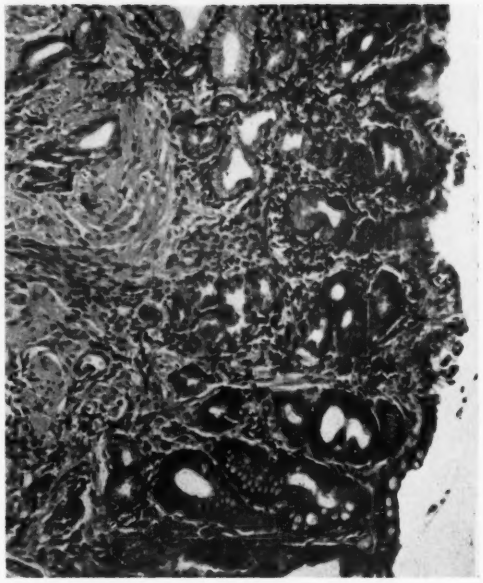

FIG. 10. Severe gastritis with considerable atrophy ('atrophic gastritis'). The mucosa is considerably reduced in width. The surface epithelium is partly irregular and partly composed of goblet cells. Similar goblet cells are seen in elongated and dilated pits in the lower part of the figure. The tubules are very much reduced in amount. Those in the centre of the figure contain a few acid- and pepsin-secreting cells, while those above are greatly dilated and composed of non-specific columnar cells. Plasma cells and polymorphs are seen throughout the substantia propria (haematoxylin and eosin, ×150)

FIG. 11. Severe gastritis with considerable atrophy ('atrophic gastritis'). Another portion of the specimen seen in Fig. 10, stained to show acid-and pepsin-secreting cells. The darkly staining cells in the superficial half of the substantia propria are both inflammatory cells and red cells, the latter probably from localized haemorrhage during biopsy procedure. A few tubules in the upper part of the figure contain acid -and pepsin-secreting cells, but the bulk of the tubules are dilated and composed of non-specific columnar cells (mucicarmine, ×150)

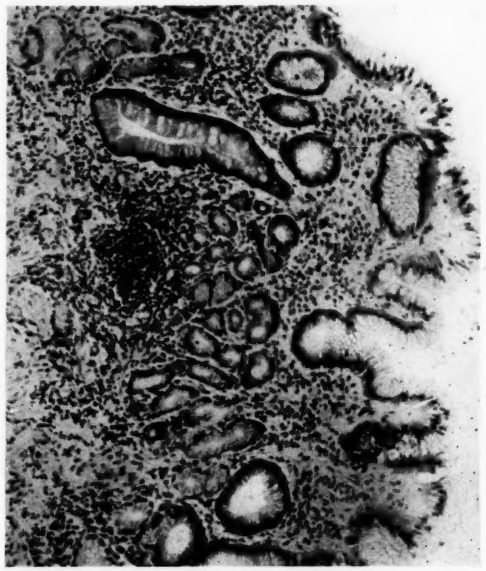

FIG. 12. Severe atrophic gastritis. In this specimen the atrophic rather than the inflammatory changes predominate. The total width of the mucosa is slightly reduced. The surface epithelium is composed of regular tall columnar cells. The pits are elongated, and one in the upper part of the figure contains numerous goblet cells. The tubules are tortuous and very much reduced in amount; special staining revealed that only an occasional tubule cell was of the acid- or pepsin-secreting type. The substantia propria contains moderate numbers of plasma cells throughout; a small lymph-follicle is seen in the centre of the figure (haematoxylin and eosin, × 150)

FIG. 13. Severe atrophic gastritis. The mucosa is considerably thinned, but the superficial portions are villous. The surface epithelium is almost entirely composed of goblet cells which stain deeply with mucicarmine. Many of the pits are elongated, largely composed of similar goblet cells, and end blindly. A few tortuous tubules are composed of acid- and pepsin-secreting cells (see Fig. 14). Infiltration of the substantia propria is slight; the predominant changes are those of atrophy (haematoxylin and eosin, × 150)

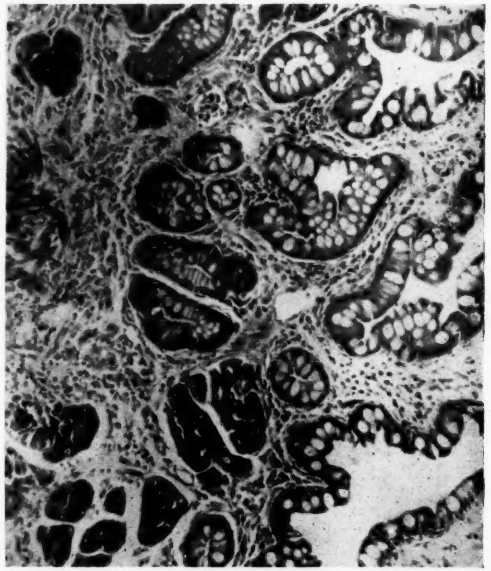

FIG. 14. Severe atrophic gastritis. The same specimen as Fig. 13, stained to show acid- and pepsin-secreting cells. The tubules seen in the lower part of the figure are those seen in a corresponding position in Fig. 13; they contain a few acid- and pepsin-secreting cells (trichrome, × 150)

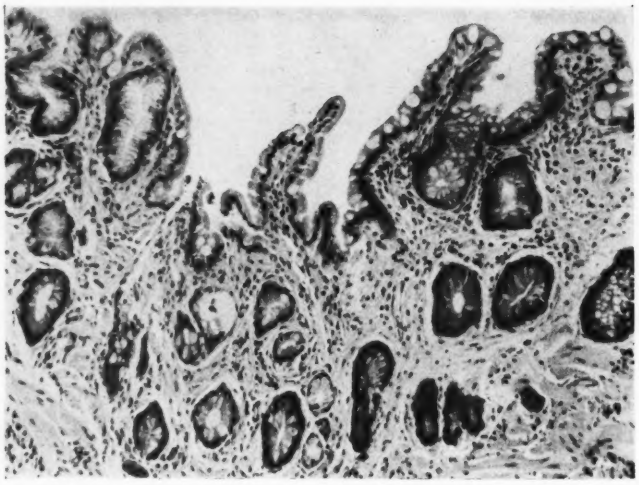

FIG. 15. Gastric atrophy. The mucosa is considerably thinned, and the superficial portions are villous. The surface epithelium and pits are largely composed of goblet cells. The pits end blindly. Only a few tubules are to be found, and these are composed of non-specific cells. There is some increase of fibrous tissue in the substantia propria, but inflammatory cell infiltration is slight (haematoxylin and eosin, $\times 150$)

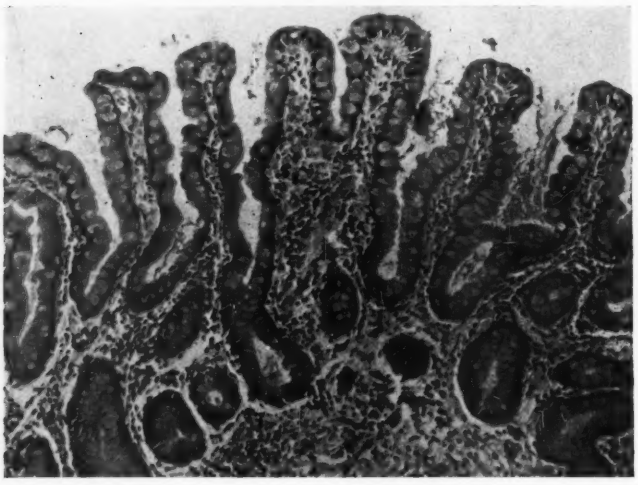

FIG. 16. Gastric atrophy. The mucosa is considerably thinned. The surface epithelium is villous and almost entirely composed of mucin-secreting goblet cells. The pits are slightly elongated and end blindly, and there is complete absence of tubules in this section. The substantia propria contains moderate numbers of plasma cells (haematoxylin and eosin, $\times 150$)

612.123:616.633.66

A STUDY BY PAPER ELECTROPHORESIS OF THE SERUM-LIPOPROTEINS IN DIABETIC AND NON-DIABETIC SUBJECTS[1]

By R. W. R. BAKER, C. L. JOINER, and J. R. TROUNCE

(From the Diabetic Clinic and the Departments of Chemical Pathology and Medicine, Guy's Hospital, London)

With Plate 35

In the last few years there has been revival of interest in the role of serum-lipids in the genesis of atheroma. Recent studies have not only shown that the serum-cholesterol concentration is on the average higher in subjects with clinical evidence of atheroma (Steiner and Domanski, 1943), but have focused attention on the physical state of the lipids in the serum and their relationship to serum-proteins. Two main methods of investigation have been used. Gofman and his colleagues have described studies of serum-lipoproteins by ultracentrifugation, and found a correlation between certain fractions of lipoprotein and the occurrence of coronary artery disease (Gofman, Jones, Lindgren, Lyon, Elliot, and Strisower, 1950). The second system of analysis depends on fractionation of the protein by means of cold ethanol followed by determination of the lipids in the various fractions. By the use of this method it has been shown that most of the cholesterol and phospholipid is combined with protein to form α- and β-lipoprotein, and further that in patients with coronary artery disease the ratio of β- to α-lipoprotein is increased (Barr, Russ, and Howard, 1951). The development of paper electrophoresis has provided a third technique for the study of serum-lipoproteins (Rosenberg, 1952; Swahn, 1952; Kunkel and Slater, 1952). By this method also it has been shown that patients with coronary artery disease show an increase in the ratio of β- to α-lipoprotein (Rosenberg, Young, and Proger, 1954). Since atheroma is a frequent cause of death in diabetics, it seemed of interest to compare the lipoprotein patterns of diabetic and non-diabetic subjects, bearing in mind that the lipoprotein pattern of both groups might well change with increasing age. The results of this comparison are reported below, together with a detailed study of the diabetic group undertaken to show any factors in this disease which may be associated with changes in the β/α lipoprotein ratio.

Experimental Study

Methods. Serum from venous blood was submitted to electrophoresis on strips of paper (Whatman 3 MM) 6 cm. wide, using barbiturate buffer (pH 8·6,

[1] Received March 31, 1955.

μ 0·03). The serum (0·15 ml.) was applied by pipette to a transverse zone near one end of a buffer-soaked strip, which was then extended horizontally between supports 26 cm. apart in a closed chamber. Electrophoresis proceeded for approximately 17 hours with 110 v. and a current of 1·5 mA., and the papers were then dried at 130° C. A strip 2 cm. wide was cut off and stained (Gurr's light green) to reveal the albumin and globulin fractions; the remaining paper was stained for lipoproteins with Sudan black (0·05 per cent. w/v in 62 per cent. v/v ethanol at 50° for three to four hours) and washed in 60 per cent. ethanol. The lipoprotein fractions were appraised in two ways. First a visual assessment was used, and the results recorded as $\alpha > \beta$, $\alpha = \beta$, $\beta > \alpha$, or $\beta \gg \alpha$. The strips were also scanned, without wetting, by a photometer from which readings of extinction coefficients were taken. In this apparatus an image of the filament of a tungsten lamp was projected through a lens and a filter (Chance ON20) on to a 2 mm. slit in a screen close to the paper. The paper was fastened over a slit 2 cm. wide in the circumference of a metal drum, which could be rotated by hand. Inside the drum and close to the paper was a photocell (Cintel GS50). Current through the photocell operated a balanced amplifier incorporating a double-triode (6SN7) wired as a cathode-follower. The least dense part of the paper was located by trial, and the resulting meter-current balanced out (zero reading); the sensitivity of the meter was then adjusted so that full-scale deflexion was obtained with dark-current (infinity reading). Readings were then taken at 0·5 cm. intervals, and the currents plotted as extinctions against displacement along the strip. On naked-eye inspection the lipoproteins fell into two main bands, and by direct comparison of the two paper strips these were identified as (1) a more rapidly moving fraction corresponding with the α_1-globulin and albumin areas, and (2) a slower fraction corresponding approximately to the β-globulins (Plate 35, Fig. 8). We have called these two fractions α- and β-lipoproteins respectively. From the photometric readings given by unstained papers a base-line was drawn on the graph, and the areas under the α- and β-lipoprotein peaks were measured with a planimeter and the β/α ratio calculated. Serum-cholesterol was determined by a modification of Bloor's method (Sackett, 1925).

Subjects Investigated

The control group consisted of healthy subjects and patients who had conditions not associated with any disorder of lipid metabolism. The diabetic subjects were out-patients attending the Diabetic Clinic, Guy's Hospital. They had, with one exception, all been under treatment for at least six months; the one exception had not yet started treatment. In all subjects the blood sample was withdrawn at about 4.0 p.m. In five subjects samples taken at this time were compared with those taken before breakfast. The average β/α lipoprotein ratio of each of the two sets of samples was the same, and no pair of samples from the same subject differed by more than 10 per cent. For the purpose of our investigation the presence of atheroma was diagnosed when there was clinical evidence of coronary-artery or peripheral vascular disease, although it

was realized that this was an inadequate index, as a severe degree of atheroma may exist without symptoms or signs. A subject was considered over-weight on a general assessment, with due allowance for height and age. The diabetic subjects were grouped on the basis of the degree of control of their disease.

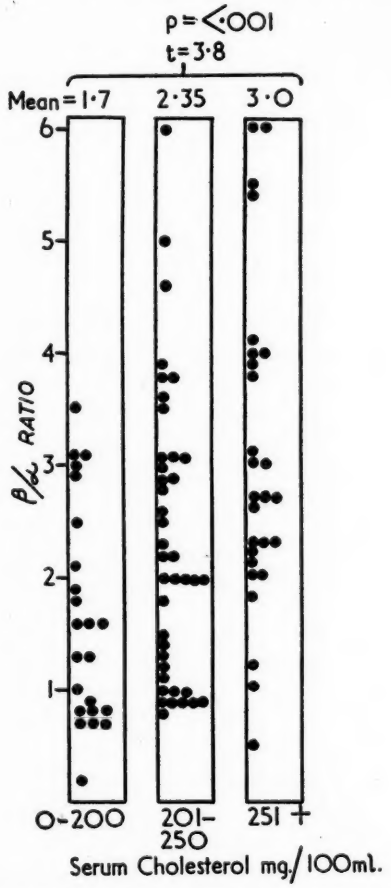

FIG. 1. The relationship between the β/α lipoprotein ratio and the serum-cholesterol in 90 subjects, both diabetic and non-diabetic. The sex of the subjects is not shown.

As an index of probability, Student's t test has been used as indicated in the figures. When t is greater than 2 (that is when the difference between the values of the two groups is greater than twice the standard error of the difference), the actual probabilities are also given.

Control was assessed by the patients' urine tests as follows ('Clinitest' tablets were used): *good*: never more than blue or green throughout 24 hours; *fair*: usually green and occasionally tan; *bad*: frequent tan colour. The blood-sugar levels throughout the day were also estimated at regular intervals.

Results

On the electrophoresis strips the albumin was displaced about 17 cm. from the origin, and the α_2-, β-, and γ-globulins were clearly visible. The α_1-globulin was in some cases not clearly separated from the albumin band owing to the

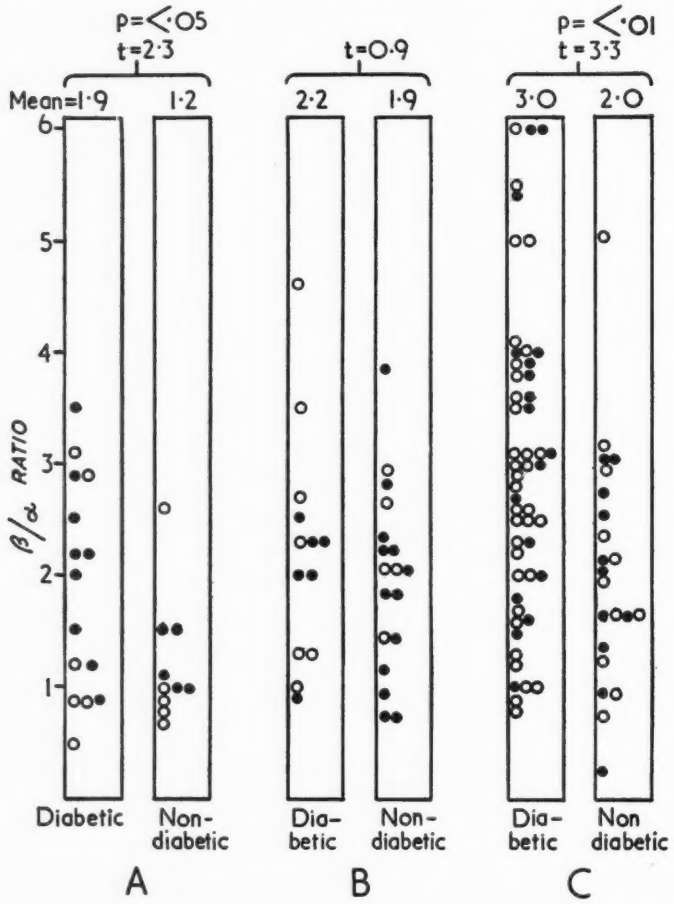

FIG. 2. A comparison between the β/α lipoprotein ratios in diabetic and non-diabetic subjects in age-groups. (*A*) aged 10 to 30 years; (*B*) aged 31 to 50 years; (*C*) aged 51 years or more.

In this and the ensuing figures male subjects are represented by a solid dot and female subjects by a circle.

large amount of serum applied to the paper to obtain adequate staining of the lipoprotein fraction. In addition to the α- and β-lipoproteins a third band of lipoprotein, near the γ-globulin, was found with some sera; in experiments on the effect of diet this extra band was shown to be associated with recent ingestion of fat, and it is possible therefore that it may be due to the presence of

chylomicrons. In normal sera the α- and β-lipoprotein fractions appeared on naked-eye examination to be approximately equal in amount; the former was often seen as two bands close together, while in some pathological sera the β fraction was similarly resolved. Photometric examination of the strips always

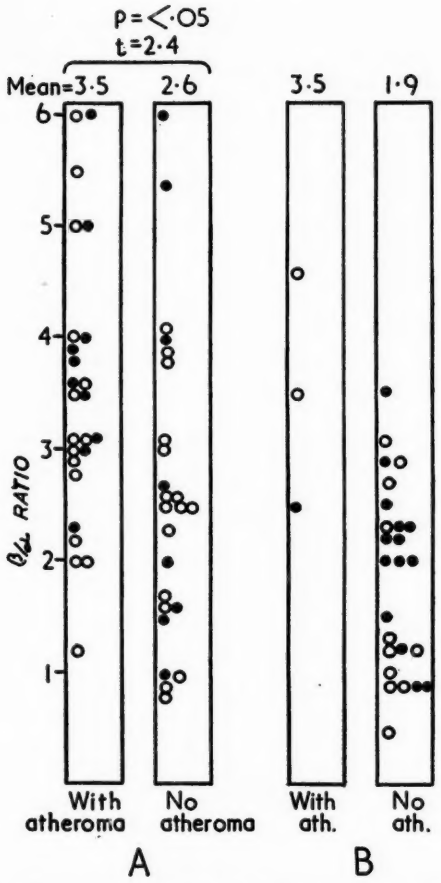

FIG. 3. A comparison between the β/α lipoprotein ratios of diabetic subjects divided as to the presence or absence of clinical atheroma, and divided into young and old age-groups. (*A*) aged 51 years or more; (*B*) aged 10 to 50 years.

revealed detail invisible to the unaided eye. The photometric results were consistent among themselves, and reproducible with any given serum. They are in accord with published data (Swahn, 1952; Nikkilä, 1952). The present method of staining and photometry, although not refined, is probably reliable to within 10 per cent., and is especially well suited to work of a comparative nature.

Relationship between β/α ratio and serum-cholesterol. Sudan black stains all types of lipid, including neutral fat, fatty acids, cholesterol, and phospholipids,

and therefore staining with this dye after paper electrophoresis gives only a general picture of the lipoprotein pattern. Most of the cholesterol is carried in the β fraction (Swahn, 1952), and it was therefore of interest to see whether an increase in the β/α ratio was related to an increase in the serum-cholesterol.

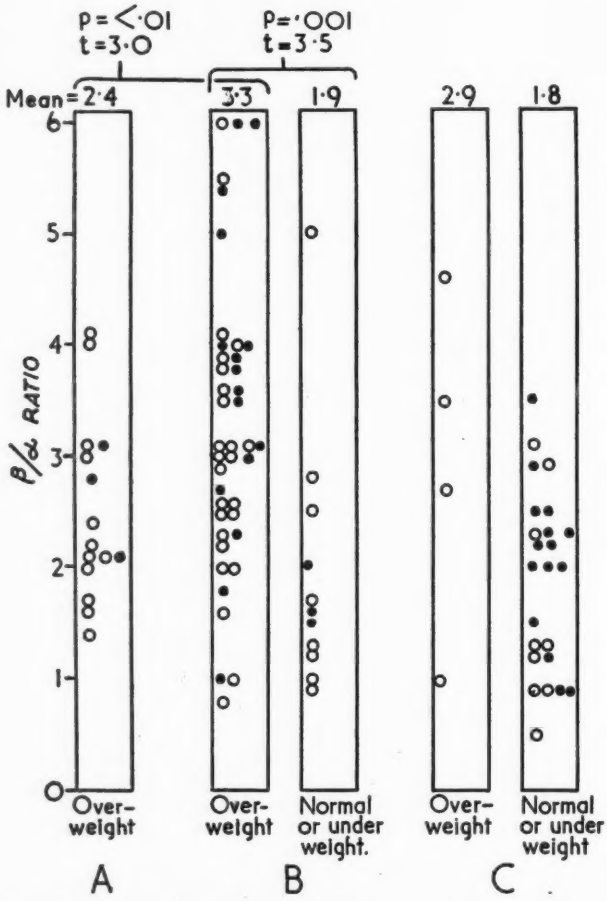

FIG. 4. A comparison between the β/α lipoprotein ratios of older and younger diabetics, subdivided on a basis of body-weight, and a group of obese elderly non-diabetic subjects. (*A*) non-diabetic subjects aged 51 years or more; (*B*) diabetics aged 51 years or more; (*C*) diabetics aged 50 years or less.

Fig. 1 shows that the average β/α ratio rises with the serum-cholesterol level, but that at all levels of serum-cholesterol there is considerable variation in the β/α lipoprotein ratio.

Comparison between β/α lipoprotein ratios in normal and diabetic subjects. Fig. 2 compares the β/α ratio in 80 diabetic and 50 non-diabetic subjects, both groups being subdivided according to age. It can be seen that the mean β/α ratio is

higher in diabetics at all ages, although the difference in the middle age-group is of doubtful significance.

Relationship between β/α lipoprotein ratio and the occurrence of atheroma in diabetic subjects. Fig. 3 shows the β/α lipoprotein ratio of 77 diabetic patients

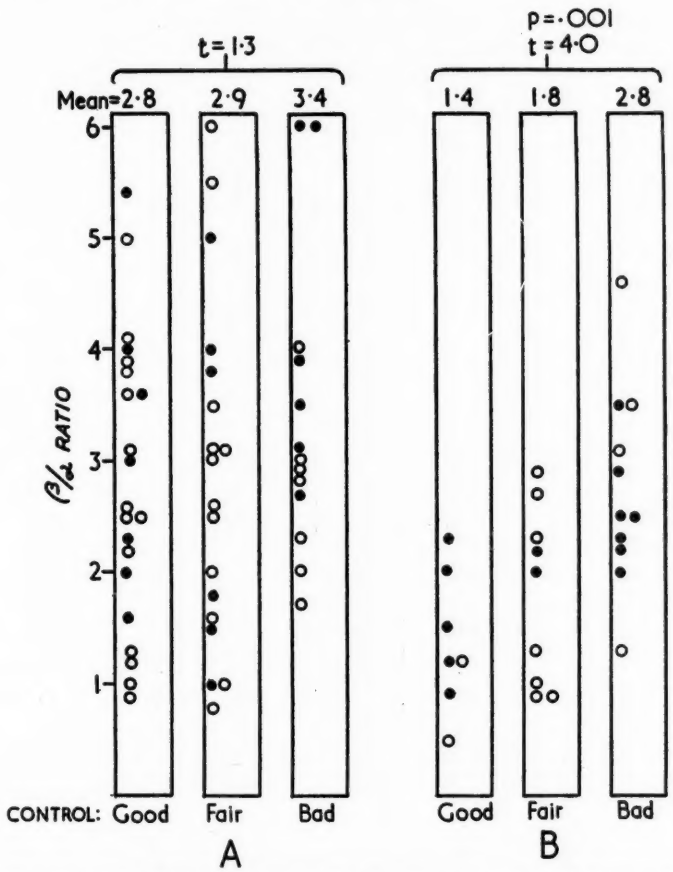

FIG. 5. The relationship between the degree of control of diabetes and the β/α lipoprotein ratio in the old and young groups of diabetics. (*A*) aged 51 years or more; (*B*) aged 50 years or less.

divided by the criterion of atheroma and also grouped according to age. In the older age-group the β/α ratio is significantly higher in patients with clinical evidence of atheroma, although there is considerable variation in both groups. In the younger group there are only three subjects with evidence of atheroma, but it is of interest that in two of them the β/α ratio is high.

Age and weight. Fig. 4 shows the effect of age and weight on the β/α ratio in diabetic patients. In the older age-group there is a significantly higher β/α ratio than in the younger group. If, however, this older group is subdivided according to weight, it can be seen that the high β/α ratio occurred largely in the obese

subjects, and that the average β/α ratio in the thin elderly subjects differed little from that found in the thin younger diabetics. A comparison of obese diabetics over 50 years old with a group of obese non-diabetic subjects of similar

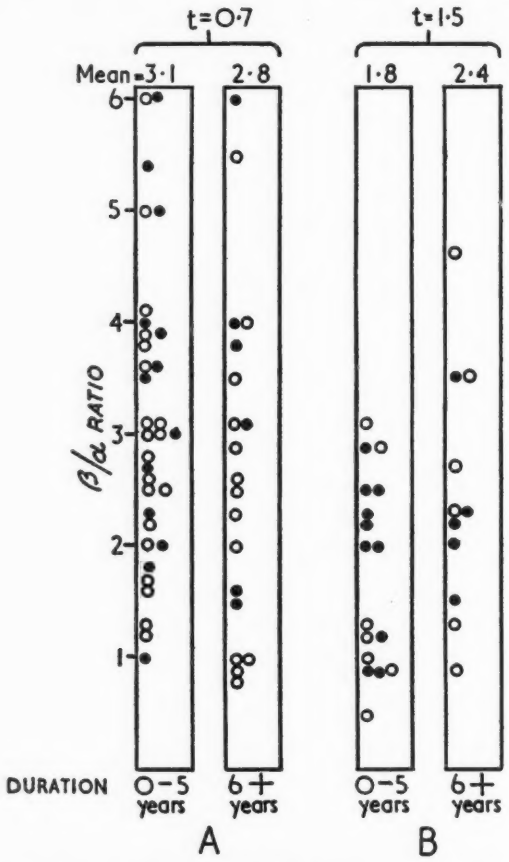

FIG. 6. The relationship between the known duration of diabetes and the β/α lipoprotein ratio in both young and old age-groups. (*A*) aged 51 years or more; (*B*) aged 50 years or less.

age shows that the β/α lipoprotein ratio is significantly higher in the diabetic group.

Degree of control. Fig. 5 shows that in the younger age-group the degree of control obtained is related to the β/α ratio; in the older age-group this relationship is of doubtful significance, although patients in whom control was considered bad show a rather higher β/α ratio.

Duration of diabetes. From Fig. 6 it can be seen that there is no significant relationship between the duration of diabetes and the β/α ratio. It must be pointed out, however, that the number of patients in this series who have had

diabetes for more than 10 years is only 13, and from such a small number it is probably unfair to draw definite conclusions.

Dosage of insulin required. Fig. 7 suggests that the β/α ratio is not related to the amount of insulin which was considered necessary to control the disorder.

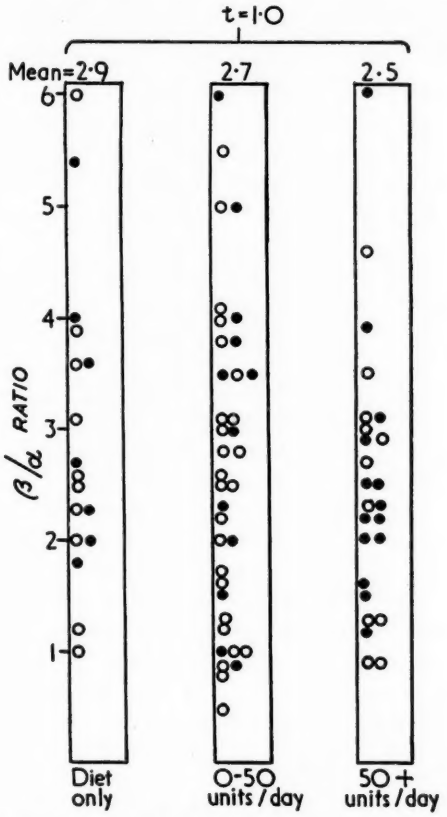

FIG. 7. The relationship between the β/α lipoprotein ratio and the number of units of insulin required daily.

Discussion

The frequent occurrence of atheromatous arterial disease in diabetes mellitus has long been recognized. It was Seegen (1870) who first reported the association of diabetes with coronary disease, and to this Heitz (1924) added intermittent claudication. The incidence of atheroma has been variably reported by a number of authors, whose conclusions have recently been tabulated and summarized (Semple, 1953). The cardiac causes of death, and the appearance of gangrene, are to be attributed almost entirely to atheroma affecting the coronary vessels and those supplying the legs. The disease of the coronary arteries seems the same as that found in non-diabetic subjects, but there is evidence

that atheroma tends to affect smaller and more distal vessels in the legs in diabetics (Semple, 1953); this would account for the old clinical observation that gangrene is commoner than claudication in diabetes. Warren and LeCompte (1952) commented that 'atherosclerosis emerges without question as the leading cause of death in diabetes, accounting for over two-thirds of all fatalities'. Although Aschoff (1933) believed that atheroma was 'super-added to the process of ageing', it was for many years regarded as an inevitable accompaniment of old age. The reasons for abandoning this attitude, and for being more optimistic, have been reviewed by Kellner (1952). It now seems possible that atheroma can be attributed in part to increased blood-lipids, particularly to increased levels of certain lipoprotein fractions, although other factors, such as species, race, and heredity, may be of importance in its occurrence, and the pressure within the vessels in its localization. Because of this association with blood-lipids, atheroma might be predicted to occur more frequently in societies living on diets rich in fats, and in those diseases in which the level of blood-lipids is known to be raised, for example diabetes mellitus, xanthomatosis, and myxoedema. And this is indeed the case.

Two points of procedure in the present investigation need comment. The first is the selection of cases. By grouping together only those patients who showed clear evidence of angina pectoris or intermittent claudication we hope to have selected only those with manifest atheroma, and to have separated them from others with retinopathy, hypertension, or Mönckeberg's sclerosis, conditions which we feel may be attributed to other causes. Secondly, by expressing the results as a comparison between the levels of two lipoprotein fractions (β/α), we hope to have avoided certain drawbacks inherent in the electrophoretic technique. From our results it appears that the average blood-lipoprotein ratios (β/α) are consistently higher in diabetic than in non-diabetic subjects. This is true at all ages, but it is most marked in patients below 30 and above 50 years of age. Furthermore, the mean values are higher in diabetics who showed clinical evidence of atherosclerosis. It seems possible that a causal relationship exists between these ratios and the occurrence of atherosclerosis. If this is the case it is important to discover what factors may influence the β-lipoprotein fraction in diabetics. It seems clear from our results that obesity is a factor predisposing to the occurrence of raised levels of β-lipoprotein, and so is the degree of control of the diabetes. There is a tendency for these values to increase with age, but sex seems to be unimportant. The severity of disease, as judged by insulin dosage, is of little moment.

Both obesity and the degree of control of diabetics can be to some extent influenced by the doctor. It is known that restriction of the fat-content of the diet is associated with a drop in the incidence of coronary disease in large non-diabetic populations (*Lancet*, 1954), and it has been shown that the serum-lipoprotein levels can be lowered by restriction of fat and cholesterol in the diet (Jones, Gofman, Lindgren, Lyon, Graham, Strisower, and Nichols, 1951). The ultimate effects of strict control of diabetes, as compared with those of a more liberal approach, have been reported from a number of sources, and all reports

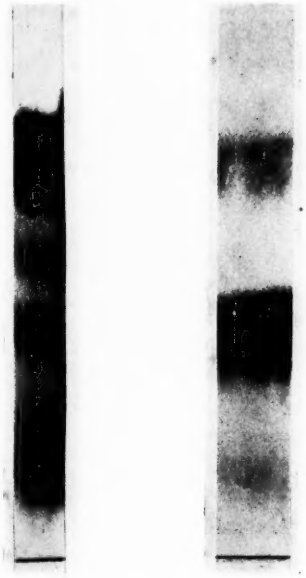

FIG. 8. Serum from a diabetic subject electrophoretically resolved on filter paper, divided, and stained with Gurr's light green and Sudan black, to show distribution of (A) proteins and (B) lipoproteins

conclude that the incidence of vascular disease is lower among patients treated strictly. Perhaps most impressive is a recent paper (Dunlop, 1954) which concludes that the careful control and aggressive treatment of diabetes mellitus over the years is a most important factor in the prevention or postponement of complications, conclusions which the present investigation is seen to support.

We should like to thank Mr. G. Clough for the serum-cholesterol estimations, Dr. Hardwick, Physician to the Diabetic Clinic, Guy's Hospital, for permission to study patients under his care, and Professor R. H. S. Thompson for his help and encouragement.

Summary

1. The lipoprotein patterns of 80 patients with diabetes mellitus and 50 non-diabetic subjects have been studied, with particular reference to the ratio between the β and α bands.

2. The lipoprotein patterns of these diabetic patients have been related to the occurrence of atheroma.

3. The lipoprotein patterns have been correlated to the age and weight of the diabetic patients, and to the degree of control, duration, and severity of the diabetes.

4. It is concluded that the β/α lipoprotein ratio is significantly higher in diabetic patients in general, and is also higher in diabetics with clinical evidence of atheroma than in diabetics without such evidence.

5. The degree of control in the younger diabetic, and the presence or absence of obesity in the older diabetic, appear to be the chief factors associated with a high β/α lipoprotein ratio.

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MATERNAL HYPERPARATHYROIDISM AND PARATHYROID DEFICIENCY IN THE CHILD[1]

With an Account of the Effect of Parathyroidectomy on Renal Function, and of an Attempt to Transplant Part of the Tumour

By JOHN BRUCE and J. A. STRONG

(From the Western General Hospital, Edinburgh, and the Departments of Surgery and Medicine, University of Edinburgh)

Severe persistent hypoparathyroidism in the child of a mother exhibiting a considerable degree of hyperparathyroidism has not been recorded before. We have recently encountered this association. The child had been under observation for parathyroid deficiency since his first year, and an account of his clinical state was published by Mitchell (1954). Briefly, he was normal at birth, when he weighed 11 pounds. He was breast-fed for nine months, and appeared to develop normally until about the age of one year. It was then noticed that his breathing became 'crowing' in character whenever he cried, and four months later he had several generalized convulsions. By the age of three and a half years a diagnosis of petit mal had been made, but shortly afterwards clear evidence of tetany was recognized, including Chvostek's and Trousseau's signs. The serum-calcium concentration was found to be 3 mg. per 100 ml., and inorganic phosphorus 7·2 mg. per 100 ml. Further study confirmed the diagnosis of hypoparathyroidism, and he subsequently responded most satisfactorily to treatment with calciferol. The mother came under our joint care for hyperparathyroidism secondary to parathyroid tumour, and we have been prompted to make this report because of the unique circumstances, and because removal of the tumour effected a remarkable improvement in renal function, which is contrary to the usual experience. Furthermore, operation on the mother provided an unusual opportunity for an experiment in gland transplantation, and portions of the maternal tumour were transferred to the child. As a result the child was rendered temporarily hyperparathyroid; but in the event the experiment was unsuccessful.

Case Report

The mother, at the age of 34 years, reported to the Out-patient Department with a complaint of thirst and polyuria, first noticed about the fourth month of her only pregnancy six years before, and sufficiently severe to arouse a suspicion of diabetes insipidus. She also complained of lack of energy, drowsiness in the evening, paroxysmal headache, and occasional vomiting in the morning. She had experienced some transient pain in the left subcostal area, and had previously noticed similar pain in the right shoulder. She was subject to emotional

[1] Received April 9, 1955.

disturbance, which she attributed to worry about her child's chronic ill health. Her previous history was irrelevant save in one respect. A year before she had noticed a swelling of the left lower alveolus, which was painless but bled freely when she brushed her teeth. Radiological examination showed destruction of the alveolar margin in the premolar and molar region, and a confident diagnosis

TABLE I

	July 1953 Before operation	*Two weeks after operation*	*July 1954*
Blood:			
Haemoglobin (%) (Haldane)	66	75	74
Red cells (millions/c.mm.)	3·43	..	4·03
Packed cell volume (%)	31	..	35
Mean corpuscular volume (c.μ)	91	..	87
Mean corpuscular haemoglobin concentration (%)	31	..	31
Reticulocytes (%)	1	1	
Sedimentation rate (mm. in 1st hr.) (Westergren)	55	50	
Plasma-proteins (gm./100 ml.) (micro-Kjeldahl)	Total 7·47 Albumin 4·43 Globulin 3·04		
Plasma-proteins: electrophoresis (Tiselius)	Normal concentrations and mobilities		
Electrolytes	See Fig. 1		
CO_2 combining power (vols. %)	41		
Alkaline phosphatase (King-Armstrong units)	14 (see Fig. 1)		
Urea nitrogen (mg./100 ml.)	12		
Urine:			
Albumin	Trace	Nil	Nil
pH	6·5	..	..
Sulkowitch test	Increased calcium	..	..
Concentration-dilution test (no fluids for 12 hours, then 2 pints of water, and urine passed hourly thereafter): specific gravity	1008–1006–1004–1004	1008–1008–1006–1008	1014–1006–1003–1002
Deposit (centrifuged)	Epithelial cells. One hyaline cast seen	..	Nothing abnormal
Culture	Negative	..	..
Urea clearance (Van Slyke) (% of normal)	48 and 45	32 and 41	..
Creatinine clearance (ml./min.)	72	..	139
Inulin clearance (ml./min.) (Olbrich, Ferguson, Robson, and Stewart, 1950)	42	..	126

of giant-cell tumour was made and apparently confirmed by histological scrutiny. The lesion responded adequately to radiotherapy. On examination she was very depressed, and wept at intervals, particularly when discussing her son's illness. An obvious swelling was visible in the right side of the neck, deep to the lower end of the sternomastoid; it was 3 cm. wide by 4 cm. long, firm, smooth, and freely movable on swallowing. She herself had not noticed it, although it was visible over the neck-line of her dress. Most of her teeth had been removed four years previously for decay, but the lower incisors were still present. There was now no evidence of a jaw tumour. Apart from some

tenderness in the left subcostal region, no other abnormality was recognized. Her blood-pressure was 140/80 mm. Hg. A specimen of urine showed a specific gravity of 1,002, with a faint deposit of albumin on heating and with salicylsulphonic acid. She was admitted to hospital, where fuller investigations followed. The results of these have been tabulated for easy comparison with those found soon after operation, and again a year later (Tables I and II).

TABLE II

Water Pitressin Test

The patient fasted from 22.30 to 06.00 hrs. At 06.00 hrs. urine was passed. The patient then drank two pints (1,140 ml.) of water, and at each subsequent hour passed urine and drank a volume of water equal to that of the urine passed. At 09.00 hrs. 10 units (0·5 ml.) of pitressin (Parke Davis & Co.) were given by subcutaneous injection. No breakfast was taken.

	August 1953 (2 weeks after operation)	*July 1954*	
Time	*Specific gravity*	*Volume (ml.)*	*Specific gravity*
06.00 . . .	1,006	350	1,014
07.00 . . .	1,008	120	1,006
08.00 . . .	1,010	400	1,003
09.00 . . .	1,008	550	1,002
Pitressin 0·5 ml.			
10.00 . . .	1,010	60	1,002
11.00 . . .	1,010	35	1,016
12.00 . . .	1,010	33	1,012
13.00 . . .	(lost)	75	1,006
14.00 . . .	1,008	150	1,005
15.00 . . .	..	100	1,005

Radiological examination of the skull showed the decalcification and fine granular appearance typical of hyperparathyroidism. There were cystic changes in the mandible, ninth rib, lower end of the left ulna, and neck of the left femur, and absorption of the lamina dura around the central incisors of the mandible. On both sides numerous fine 'spots' of calcification were scattered irregularly throughout the renal areas.

The *diagnosis* was obviously that of hyperparathyroidism, with early generalized osteitis fibrosa and nephrocalcinosis with impaired renal function, and the obvious cause a tumour of the right lower parathyroid gland. Operation was therefore advised, and a decision made to transplant portions of the tumour to the child as soon as it was resected.

Operation 21.7.53. A soft crumbling mass of purple tissue, measuring approximately $3 \times 2 \times 1$ cm., was discovered in the position of the right inferior parathyroid, behind the right lower pole of the thyroid gland; it weighed approximately 7·8 gm. Immediately after its piecemeal removal a series of fragments, weighing 1·11 gm., were implanted into the marrow cavity of the upper end of the child's left tibia through a half-inch trephine hole, and 2·34 gm. were inserted into the left rectus abdominis muscle.

Histological report on tumour. The adenoma was composed mainly of cords and masses of 'principal cells'. Scattered throughout the tumour were acini containing a colloid-like coagulum, resembling that sometimes produced by normal parathyroid tissue. There was great vascularity, congestion, and oedema. The cell type appeared to be intermediate between the usual 'principal' (clear) cell and the oxyphil type, with the former predominating.

Progress. The mother's subsequent progress was most satisfactory. Apart from some transient tingling she had no symptoms and, although Chvostek's sign was weakly but definitely positive four days after operation and for two weeks thereafter, Trousseau's sign never appeared. The metabolic changes are shown in Figs. 1 and 2 (pp. 314–15). One year after operation she felt very well, apart from occasional nocturnal cramp. Her thirst and polyuria, which persisted for a time after operation, had by then entirely disappeared, and emotionally she was very greatly improved. The serum-calcium concentration was 10·1 mg. per 100 ml., serum inorganic phosphorus 3·3 mg. per 100 ml., and alkaline phosphatase 6 King-Armstrong units. Radiological examination now showed the skull to be normal. The ulnar cyst persisted, but its edge was more dense, and the nephrocalcinosis was unchanged.

The child. Shortly after operation the child developed a hypercalcaemia so profound that removal of the transplants was contemplated. With the onset of diuresis, however, the serum-calcium concentration diminished rapidly. Unfortunately by five weeks after the operation the serum-calcium concentration had fallen to 8·5 mg. per 100 ml., and treatment had then to be resumed. His subsequent progress, on a high-calcium, low-phosphorus diet with vitamin D, has been satisfactory, and there is no evidence that the transplants had any effect other than the marked temporary changes illustrated in Fig. 3 (p. 317).

Discussion

1. *The relation of maternal hyperparathyroidism to hypoparathyroidism in the offspring.* Observations on the simultaneous occurrence of parathyroid disturbances in mother and child are few. Gerloczy and Farkas (1953) reported a case of neonatal osteitis fibrosa cystica, with hyperplasia of all the parathyroid glands, in the child of a mother who for 20 years had suffered from hypoparathyroidism; but the association of lasting hypoparathyroidism in the child of a hyperparathyroid mother appears to be unique. The coincidence is unlikely to be fortuitous, for both are rare conditions, and furthermore reciprocal disturbances are known to occur as transient phenomena both in man and in animals. Thus hypocalcaemic tetany has been reported by Friderichsen (1939) in a breast-fed infant aged five months, whose mother at the time was the victim of hyperparathyroidism due to a parathyroid adenoma. Two months after weaning the serum-calcium concentration had risen from 6·7 to 9 mg. per 100ml., and there was no further tetany. It was suggested that the excess of maternal parathyroid hormone had suppressed the development of the infant's parathyroids for so long as it received the mother's milk. When the child was given cow's milk the increased intake of phosphorus precipitated tetany, but with the termination of breast-feeding the parathyroid glands apparently became sufficiently active within two months to maintain normal serum-calcium, although the serum-phosphorus concentration at that time was as high as 8 mg. per 100 ml. This explanation is not convincing; parathyroid hormone is inactive by mouth, and in any event it is difficult to believe that enough could pass in the breast-milk to arrest the development of the child's parathyroid glands, and at the same time allow a low serum concentration of calcium to persist. The amount of calcium in the serum frequently falls considerably immediately after

birth (Bakwin, 1939; Denzer, Reiner, and Weiner, 1939), with the appearance of 'neonatal tetany'. This is a transient phenomenon, however. Talbot, Sobel, McArthur, and Crawford (1952) reported two infants with hypoparathyroidism whose mothers were hyperparathyroid, but even in them the condition was transient (Talbot, 1953).

Hoskins and Snyder (1933), in experiments on pregnant bitches, found that injections of parathyroid hormone into the foetuses in utero raised the foetal serum-calcium concentration considerably without affecting the maternal concentration. When the hormone was injected into the mother the serum-calcium concentration rose in both parent and foetus, but to a less extent in the latter. They concluded that there was no evidence of placental transmission of parathyroid hormone. Schwartzer (1940) found that when parathyroid hormone was given by injection to pregnant rats the offspring showed considerably reduced serum-calcium concentration shortly after birth. Sinclair (1942), also working with rats, demonstrated that the foetal parathyroids were depressed by an excess of maternal serum-calcium or of parathyroid hormone, and that conversely a low serum-calcium or high serum-phosphorus concentration in the mother led to parathyroid hyperplasia in the foetus. The evidence is insufficient to show whether foetal hypoparathyroidism is directly due to a high maternal serum concentration of calcium, or in part or directly due to an underlying excess of parathyroid hormone. The evidence of Hoskins and Snyder (1933) favours the view that the transmission of parathyroid hormone from foetus to mother is unlikely, and suggests that it is the change in the calcium and phosphorus of the maternal serum that influences the foetal parathyroids, and that the maternal hormone can act only indirectly by way of this mechanism.

In the present instance it seems possible that the development of the child's parathyroid glands in utero was suppressed by the excess of diffusible calcium in the mother's serum, and that in contrast to their usual behaviour the glands failed to recover when the suppressive stimulus was withdrawn. If this is so, it is probable that the absence of declared hypoparathyroidism during the first year of life was due to a low-phosphate and high-calcium diet, and possibly vitamin D in relatively large quantities; with an increase of dietary phosphorus the latent tetany became overt. As Mitchell (1954) indicated in his report, the child suffered from unilateral multicystic disease of the kidney. It is unlikely that both this and the parathyroid disorder were due to a genetic defect, but in view of the known propensity of some maternal diseases to induce congenital defects in the offspring, such as cataract and congenital heart disease, it is remotely possible that both the renal disease and the hypoparathyroidism were the result of maternal hyperparathyroidism.

2. *The parathyroid transplantation.* The failure of the transplanted parathyroid fragments to 'take' was consistent with previously recorded experience. There was no likelihood, and in the event no opportunity, of establishing an immediate vascular link between the tissue of the host and the grafts, which is the most certain means of ensuring survival. The alternative to immediate vascularization—the secondary acquisition of a blood supply—demands either

the survival of the transplant while the phenomenon is occurring, or at least the survival of some of it from which regeneration can subsequently take place. This at the best is an unpredictable and chancy process, and previous attempts have been notoriously unsuccessful. Kooreman and Gaillard (1950) attempted the transplantation of parathyroid tissue from newborn infants in 29 patients with hypoparathyroidism, which in 27 cases had followed operation. Before the actual transference the neonatal parathyroid tissue was grown for some time in media prepared from the serum of the recipient; but even with this precaution there was apparent success in only seven patients, and in these the evidence of a successful 'take' is by no means unequivocal. Improvement may well have been the result of spontaneous resumption of activity on the part of remaining but temporarily depressed parathyroid tissue; and a similar explanation may account for the claim by Peycelon and Guillemin (1946) that they had successfully transplanted parathyroid tissue from a 29-year-old hyperparathyroid patient to a 63-year-old patient who had tetany after operation. It was further disappointing to learn, in the present instance, that the mother and child belonged to different blood groups. Even so, by transference from mother to son we had hoped that something nearer to an autograft would be achieved than in the case of unrelated host and donor. This hope was not fulfilled. The grafts themselves obviously contained a considerable amount of hormone, which had a profound though temporary effect on the child's calcium metabolism; but after some weeks, when the hormone-content of the transplants was exhausted, the signs of hypoparathyroidism quickly reappeared.

3. *Renal function.* The effects of the hyperparathyroidism, and of the subsequent operation, on the mother's renal function were in certain respects remarkable. Initially, when the daily excretion of urine was five litres or more, the clinical state resembled diabetes insipidus. The fixed specific gravity of the urine, the evidence of renal function tests, and the radiological appearance of nephrocalcinosis all indicated severe renal damage. The natural assumption—that this damage was due to a direct effect of parathyroid hormone, and would improve after parathyroidectomy—was apparently denied by the course of the case immediately after operation. During the subsequent 24 hours the urinary output was only 60 ml., and on the succeeding day less than a litre, although the fluid intake was adequate and there was no abnormal loss by vomiting or by the bowel. This initial water retention might have been due to endogenous vasopressin, increased adrenocortical activity, or withdrawal of an excess of parathyroid hormone; later, when the urine was again large in volume and of low concentration, the response to 'pitressin' by injection suggested insensitivity to vasopressin; and absence of dilution in response to 'water load', and continued low specific gravity, seemed explicable only on a basis of renal tubular damage. Nevertheless, the rapid disappearance of calcium from the urine indicated that after 24 hours the kidney was no longer subject to the influence of excessive circulating parathyroid hormone. After these initial disappointments it was gratifying, a year later, to find a substantial improvement in renal function reflected in all the tests applied (Table I), and especially in inulin and

creatinine clearances, and this despite the absence of change in the degree of renal calcification. This improvement cannot be attributed directly to withdrawal of the excess of parathyroid hormone, which as an immediate effect of operation might have been expected to provide a rapid and striking response. It must represent either repair of damaged renal structures or an indirect effect of hormone withdrawal. Such improvement is in striking contrast to the usual deterioration of function after operation in patients with advanced nephrocalcinosis, and is probably due in large measure to the absence of urinary infection. To this also may be attributed the absence of stones in spite of the high excretion of calcium by the kidney, though the dilution of calcium in the large volume of water secreted was an important additional factor.

Albright and Reifenstein (1948) have reported a patient with hyperparathyroidism simulating diabetes insipidus, whose renal function in many respects resembled that of our patient. Her fluid intake varied between four and seven litres daily, the specific gravity of the urine varied between 1,001 and 1,010, and in concentration tests, which included the injection of 10 i. u. of pituitrin, no improvement was achieved, except on one isolated occasion when the specific gravity rose to 1,014. Glomerular filtration was above 50 per cent., renal blood-flow about 60 per cent., and tubular maximum capacity to secrete diodrast about 60 per cent. of normal. One week after operation the power of urine concentration was still limited to a specific gravity of 1,006, and 1,012 after pituitrin, but a year later she was able to concentrate to a specific gravity of 1,018 after 0·5 ml. of 'surgical pituitrin'. Roussak and Oleesky (1954) described two patients, under the title of 'water-losing nephritis', whose polyuria and polydipsia failed to respond to the injection of pitressin. In one the condition was associated with the renal changes sometimes found in myelomatosis, but without hypercalcaemia; in the other with carcinoma of the prostate and moderate bladder distension. Three and a half months after resection of the prostate the response to pitressin was again normal. Black (1953), reviewing records of 112 cases at the Mayo Clinic, pointed out that in fact renal damage may be progressive in spite of correction of the hyperparathyroidism. In our opinion the outcome depends largely on the presence or absence of urinary infection, and in this respect our patient was more fortunate than most.

4. *The plasma-proteins.* Martin and Perkins (1951) suggested that the serum of patients with active parathyroid tumours contained an increased amount of albumin with a high calcium-binding capacity, and that this might account for some of the changes in circulating calcium found in this disorder. Later (1953) they described an increase in the calcium-binding capacity of serum-albumin in patients with parathyroid tumours, which reverted to normal after removal of the tumour, except in patients who showed evidence of renal damage. They found similar changes in 10 patients with chronic renal disease unrelated to hyperparathyroidism. Electrophoresis of the plasma from our patient showed normal mobilities and concentrations of the plasma-protein fractions. The calcium-binding capacity of the serum-albumin was not examined; but if the belief is confirmed that this test is abnormal in the presence of renal disease,

it may prove of value in predicting the outcome of operation in hyperparathyroidism.

5. *Metabolic changes in the mother.* Metabolic studies were carried out for approximately two weeks before and after operation in an effort to determine whether the protracted hyperparathyroidism, the persistent diuresis, and the impaired renal function in any way modified the patient's response to removal

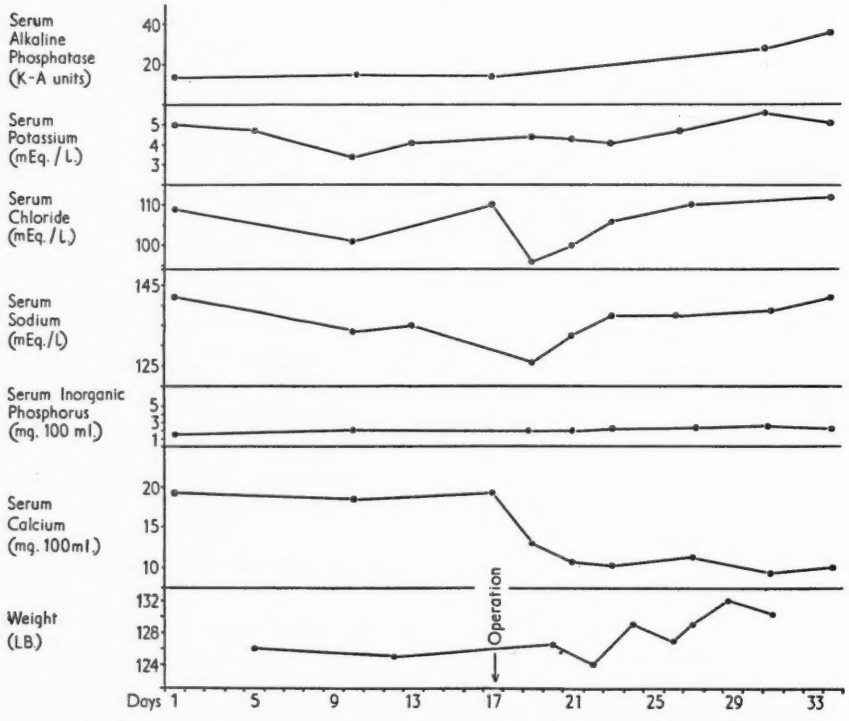

FIG. 1. Metabolic changes in the mother associated with removal of a parathyroid adenoma.

of the parathyroid adenoma. The data are shown graphically in Figs. 1 and 2.

(1) *Water.* The profound diuresis before operation was at once arrested by the removal of the adenoma, only to return with but slightly abated vigour within a week. A single observation later suggested that the patient was relatively insensitive to the antidiuretic hormone. That the patient had in fact been chronically under-hydrated is suggested by her gain in weight of 4·5 lb. (2 kg.) in the few days following operation, when diuresis was not so vigorous.

(2) *Electrolytes.* The sodium, chloride, and potassium balance is based on an intake calculated from tables (McCance and Widdowson, 1946), but excretion of these ions in the stools was not measured. The patient had 11 motions without diarrhoea in the 14 days after operation, so that losses in the stool are unlikely to have formed more than a small proportion of the total balance.

With these reservations, the balance suggests that the patient was depleted of sodium and chloride before and immediately after operation, as the balance was positive while her weight continued to increase. The retention of sodium appeared to be considerably greater than would be required for the formation

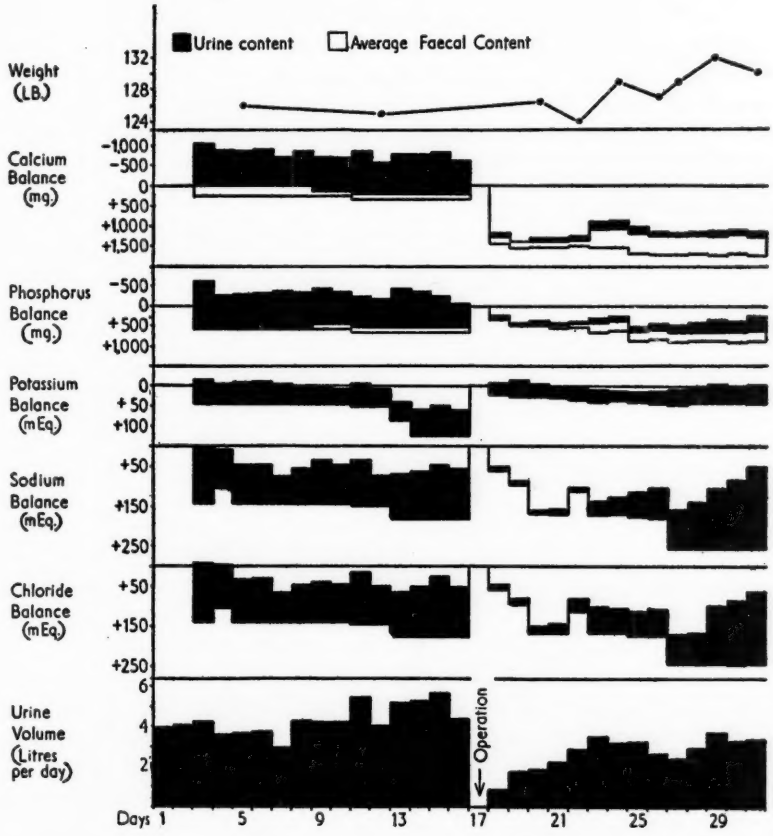

FIG. 2. Urine volume and electrolyte changes in the mother before and after removal of the parathyroid adenoma. The daily electrolyte intake is charted downwards from the base line, and faecal excretion is then shown as a clear area extending up towards the base line from the lowest part of the intake block. Above this the urine electrolyte content is shown as a black area. A positive balance is therefore represented by a clear area between the base line and the upper border of the dark block representing urine content. A negative balance is shown by the extent to which the output lies above the base line.

of the two litres of extracellular fluid which induced a gain in weight of 2 kg. Shelling, Kajdi, and Guth (1938) have described a loss of chloride and fixed base, as well as of water, in dogs given repeated injections of parathyroid hormone. Recalling our patient's unusually high serum-calcium concentration, we must assume that the adenoma was forming and liberating large amounts of

hormone, so that similar effects on electrolytes other than calcium and phosphorus would not be surprising. An increase in the intake of sodium chloride on day 27 was followed by a brisk increase in the urinary output of both ions, suggesting that the previous depletion of body stores of sodium and chloride had by then been corrected. The early fall in serum-sodium and serum-chloride concentration after operation was probably entirely due to water retention.

Potassium depletion has also been described in hyperparathyroidism (Böttiger, 1954). In our patient the potassium balance was slightly negative before operation in spite of an average intake. A low serum-potassium concentration was found a few days before operation, and the intake of potassium was then doubled. The extra intake was all retained, so that it seems that, as in the case of sodium, the body potassium was also depleted. It seems probable that the negative potassium balance and the positive sodium balance immediately after the operation are both in part an expression of the normal metabolic response to operation (Wilkinson, Billing, Nagy, and Stewart, 1949).

(3) *Calcium and phosphorus.* The large losses, almost exclusively in the urine, of calcium and phosphorus, in the face of a very low intake, are usual findings in hyperparathyroidism. Although this considerable loss of calcium must have been in progress for a long time, the balance cannot have been unduly unfavourable, as otherwise the evidence of skeletal demineralization would have been more pronounced. In the two weeks before operation, on a very low intake, the patient was losing an average of 870 mg. of calcium per day in the urine alone, and losses of this order would certainly have produced more striking radiological changes. The profound and rapid fall in the serum concentration of calcium after operation is of particular interest in relation to the action of the parathyroid hormone. In 48 hours the serum-calcium fell from 19·2 to 12·8 mg. per 100 ml., a difference of 6·4 mg. If this change is assumed to have affected the diffusible calcium alone, it represents a loss from the blood and extracellular fluid of approximately 770 mg. In this period only 65 mg. of calcium were excreted in the urine, and, as the average daily loss of calcium in the stools at this time was 187 mg., most of the fall of concentration in the serum must have been occasioned by the return of calcium to the bones. This fact strongly supports the view that the primary action of parathyroid hormone is on the mobilization of skeletal calcium, and not on its renal excretion (*Lancet*, 1953). The brisk antidiuresis immediately after operation, while the serum concentration of calcium was still raised, suggests that the parathyroid hormone itself was responsible for the pre-operative diuresis. The later polyuria was probably due in part to renal tubular insufficiency, and in part to unresponsiveness to the antidiuretic hormone.

(4) *Alkaline phosphatase.* Pugh (1953), in a study of 112 cases observed at the Mayo Clinic, found that the serum concentration of alkaline phosphatase was raised in all patients who showed radiological changes in bone, but was normal in the others. Indeed, he postulated that if the concentration of serum alkaline phosphatase is normal, then radiography is superfluous. Contrary to this experience, in spite of the high-grade hypercalcaemia and the radiological and

other evidence of over-production of parathyroid hormone, the alkaline phosphatase level was relatively normal in our patient, and only rose some time after operation, to return once more to normal three months later. This circumstance may well have helped to prevent overt tetany after operation. The normal serum alkaline phosphatase suggests that osteoblastic activity was not increased, and so calcium and phosphorus would not continue to be removed unduly

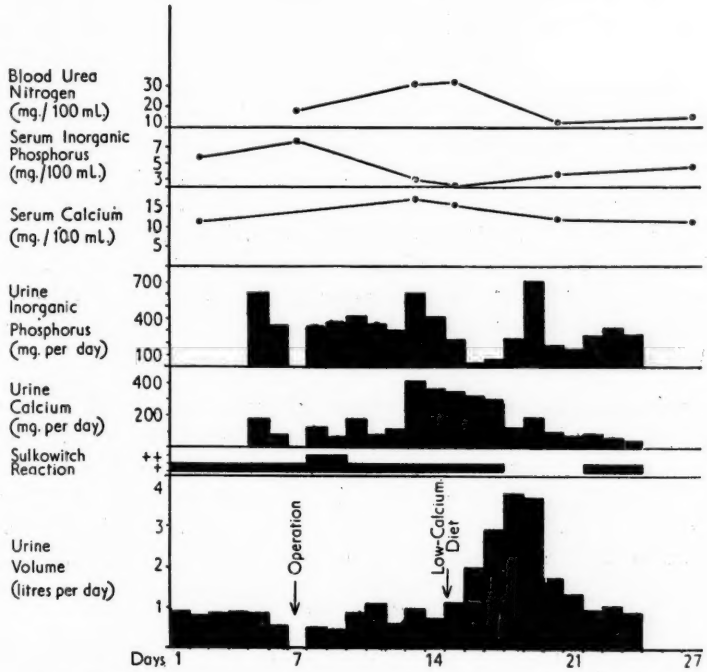

FIG. 3. Metabolic changes in the hypoparathyroid son associated with the transplantation of part of his mother's parathyroid adenoma. He had been receiving 50,000 units of vitamin D and 2 gm. of calcium lactate daily by mouth until shortly before the observations began. Throughout the period shown he received no vitamin D or calcium lactate. For several reasons no attempt was made to fix his intake of food and fluids, which were given *ad libitum*. The urine collections on days 7, 8, and 9 were not complete.

rapidly from the circulation to provide for recalcification. For a brief period after operation calcium was very rapidly diverted from the serum until its concentration fell to normal, but this change appears to have been due to withdrawal of excess of parathyroid hormone. In any case it was hoped to minimize the chances of tetany by a high-calcium, low-phosphorus diet. In fact, Chvostek's sign became weakly positive, but Trousseau's sign never appeared, and the patient was spared the discomfort of spasmophilia.

6. *Metabolic changes in the child.* The limited scope of metabolic studies in the case of the child was sufficient to indicate certain striking effects of operation.

In the first place, the transplanted material (3·4 gm.) obviously contained a large amount of hormone, and the child was capable of responding briskly to it, thus confirming the positive result of the Ellsworth-Howard test performed earlier (Mitchell, 1954). Both responses serve to distinguish the child's disorder from the pseudohypoparathyroidism described by Albright, Burnett, Smith, and Parson (1942), although the validity of the Ellsworth-Howard test has recently been questioned by Dent (1954) on the grounds that the responses of normal subjects to repeated injections of parathyroid hormone are inconsistent. As the serum-calcium concentration rose, the phosphorus concentration showed the usual reciprocal fall. The blood urea nitrogen rose, and fell again when a diuresis was established. It is usually stated that an early and marked effect of the administration of parathyroid hormone is a brisk diuresis of phosphorus, followed by an increase in the excretion of calcium. In our patient the transplantation was not followed by an appreciable change in phosphorus excretion, although the serum concentration fell profoundly. The concentration and output of calcium in the urine were increased approximately threefold, but only after several days; water diuresis was delayed even further, and was at its maximum only after the calcium excretion had returned to its previous normal level.

We are indebted to Mrs. E. K. Dawson for her report on the histology of the tumour, and to Dr. H. J. Cruft, of the Department of Biochemistry, University of Edinburgh, for the serum electrophoresis. We should like to thank Dr. S. L. Tompsett and the staff of the Biochemical Laboratory, Edinburgh Northern Group of Hospitals, for part of the biochemical work involved, and Dr. J. S. Robson, who kindly arranged the inulin and creatinine clearances.

Summary

1. The association of hyperparathyroidism in a woman and persistent hypoparathyroidism in her child is reported for the first time.

2. Transplantation of part of the parathyroid adenoma from mother to child is described.

3. The metabolic effects of the disorder in the mother, and of removal of the parathyroid adenoma, are described and discussed.

4. A limited account is given of the temporary effects of the transplanted parathyroid tissue in the child.

5. The possibility of maternal disease might be considered in any case of juvenile idiopathic hypoparathyroidism.

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MASSIVE DIVERTICULOSIS OF THE SMALL INTESTINE WITH STEATORRHOEA AND MEGALOBLASTIC ANAEMIA[1]

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With Plates 36 and 37

Since Badenoch and Bedford (1954) first described two cases of massive diverticulosis of the upper intestine presenting the syndrome of steatorrhoea and megaloblastic anaemia, a third case has been reported (Dick, 1955). The purpose of the present paper is to report additional observations on the one survivor of the two original patients and on three others, and to put forward further evidence for the view that the diverticulosis of the small intestine is responsible for both the steatorrhoea and the megaloblastic anaemia.

Incidence

Astley Cooper (1804–7) was the first to describe the condition of jejunal diverticulosis, and since then well over 200 cases have been reported (Edwards, 1939, 1954; Benson, Dixon, and Waugh, 1943; Walker, 1944–5; Hillemand, Chérigié, Rosenstiel, and Iglesias, 1951). Nevertheless, massive diverticulosis is an uncommon condition, occurring as an incidental finding at post-mortem examination in from 0·1 to 0·2 per cent. of all autopsies (Hillemand, Chérigié, Rosenstiel, and Iglesias, 1951), or rather more commonly—0·3 per cent.—in people dying over the age of 50 (Bedford, unpublished observations). The diverticula are often difficult to demonstrate radiologically, but the incidence reported in several large series of barium meals (0·06 per cent., Edwards, 1954; 0·1 per cent., King, 1949–50; 0·24 per cent., Dneprovolzhskii, 1953) agrees well with the findings at necropsy. The condition is slightly more common in men than in women over the age of 50 (Hillemand, Chérigié, Rosenstiel, and Iglesias, 1951). Edwards (1954) has put forward reasons for believing that the diverticula are acquired and not congenital.

Natural history of diverticulosis of the small intestine. The majority of patients with jejunal diverticulosis have no symptoms, but complications which have been reported include abdominal pain, vomiting, intestinal obstruction, perforation, adhesions, and haemorrhage. Diarrhoea has been described occasionally (Guthrie and Hughes, 1937; Benson, Dixon, and Waugh, 1943; Wilkerson and Coffman, 1948; Orr and Russell, 1951–2; Dneprovolzhskii, 1953; Edwards, 1954), but never steatorrhoea, although in one case with diarrhoea a single

[1] Received April 23, 1955.

estimation of the fat in the stool had given a high result (39·6 gm. per cent.; Montuschi, 1949). Iron-deficiency anaemia is occasionally associated with jejunal diverticulosis, but megaloblastic anaemia is very rare (Taylor, 1930; Krevans, Lockard-Conley, and Sachs, 1954; Spang, 1954). Wilkinson (1955) has reported one patient with a spontaneous ileocolic fistula, steatorrhoea, and a megaloblastic anaemia, who was found at operation to have jejunal diverticulosis. The triad of jejunal diverticulosis, steatorrhoea, and megaloblastic anaemia is very unusual. The four cases reported here and the one recorded by Dick (1955) appear to be all that are to be found in the literature.

Case Histories

Case 1 (Radcliffe Infirmary No. 73710/47). Farmer. Age at death in 1952, 64 years.

This patient was quite well until May 1946 when, at the age of 58 years, he suddenly developed diarrhoea and abdominal discomfort. So sudden was the onset that he attributed the symptoms to food poisoning, but no one else in the household was affected at the time, and the diarrhoea continued with the passage of two to 12 loose, pale, foul motions each day. There was neither blood nor mucus in the stools. A year later he began to tire easily, and his friends noticed that he was pale. He developed spontaneous cramps in his limbs, and his tongue became sore, especially after smoking his pipe. Formerly a kindly, placid, and tidy man, he became morose and quarrelsome, and careless of his appearance and habits. In June 1947 he was admitted to hospital. On examination he was pale and emaciated. The tongue was smooth, with atrophic papillae. The hair and nails were normal. The blood-pressure was 150/85. Latent tetany was present, both Trousseau's and Chvostek's signs being positive. There were no petechiae or bruises in the skin, and the lymph-nodes were not enlarged. The abdomen was distended, and contrasted sharply with the thin limbs and trunk and sunken cheeks, but it was not tender, and no masses could be felt in it. The urine was normal.

Investigation revealed a moderate macrocytic anaemia: haemoglobin 11·9 gm. per 100 ml., red blood-cells 3·84 million per c.mm., and colour index 1·1. The marrow was megaloblastic, and the test meal showed histamine-fast achlorhydria. The faeces contained no occult blood. A fat balance (four days) demonstrated that only 82 per cent. of the daily dietary intake of fat was being absorbed. The pancreatic response to secretin was normal, and the excretion of nitrogen in the faeces was 2·1 gm. daily. The oral glucose-tolerance test gave a normal result. The total plasma-proteins were 5·9 gm. per 100 ml. (albumin 3·6 gm. per 100 ml.). The serum-calcium was 7·6 mg. per 100 ml., serum-phosphate with the patient fasting 2·3 mg. per 100 ml., and serum alkaline phosphatase 9 King-Armstrong units. A barium meal revealed a diverticulum of the duodenum and what was taken to be flocculation of barium in the small intestine; but in retrospect it seems that the clumps of barium may well have been in the diverticula which were demonstrated *post mortem*. These clumps of barium were still visible when the patient was screened again two days later.

From the first his management proved difficult. He was given a high-protein, low-fat diet with added vitamins and calcium, and the anaemia was treated with liver extract. The response to parenteral liver was incomplete, but later folic acid was added and the haemoglobin returned to normal. He would not comply with his dietary instructions, and for long periods gave up treatment altogether,

only to return to it when his condition was perilous. In 1949, three years after the onset of the illness, he had unexplained melaena. X-rays taken at the time failed to reveal the source of the haemorrhage, and the prothrombin time was normal. In 1950 he developed generalized oedema with hypoproteinaemia, and in 1951 he had an attack of colic and vomiting, which lasted five days and appeared to be due to subacute intestinal obstruction. He suffered frequent paroxysms of abdominal pain, lost weight steadily, and finally, in January 1952, died of bronchopneumonia.

Post-mortem examination revealed extensive diverticulosis of the upper part of the small intestine (Plate 36, Figs. 2 and 3). The diverticula extended almost continuously from the second part of the duodenum along the upper three feet of the jejunum, with others scattered more distally. Apart from one in the second part of the duodenum, all the diverticula were on the mesenteric border of the intestine. They varied in size from one to four and a half inches in diameter, were thin-walled, and communicated with the lumen of the intestine by openings up to one inch in diameter. The pouches and the upper part of the intestine were filled with a turbid, watery fluid. The lungs showed the expected bronchopneumonia, but all the other organs were natural.

During the course of his illness four barium-meal examinations were carried out; all revealed the diverticulum of the duodenum, but the massive jejunal diverticulosis was not suspected. In retrospect 'levels' of opaque medium, which were considered to be indicative of a small-bowel obstruction, were certainly in the diverticula. Most of the diverticula filled poorly or not at all, yet opaque medium remained in the pouches for at least two days on two occasions.

Case 2 (Radcliffe Infirmary No. 162686). Housekeeper, aged 70 years.

Her past history is interesting in that she had suffered from a severe anaemia at the age of 15 years, and at 25 developed lupus vulgaris on the face. Apart from these illnesses she had remained well and active until 1949, when at the age of 64 she suddenly began to have pain in the abdomen and lower chest. This pain could be brought on by stooping or by eating fatty foods, and at times radiated up into the neck and down both arms. She suffered from waterbrash, and was often nauseated. Two years later she began to suffer from flatulence and a painless diarrhoea. The stools were pale and watery, and contained neither blood nor mucus. Her condition gradually deteriorated; she developed paraesthesiae of the fingers, cramps in the legs, shortness of breath, and oedema of the ankles. She lost two stone in weight. In August 1952, three years after the illness began, she was admitted to hospital. On examination she was thin and pale, with a dry, pigmented skin. The blood-pressure was 140/80. The scars of healed lupus vulgaris were present on her face. The tongue was pale, but the papillae were not atrophic; a few petechiae and bruises were present on the arms and upper chest. The abdomen was tympanitic and distended, but otherwise normal. There was no enlargement of the lymph-nodes. The urine was normal.

Investigation revealed that she had a moderate macrocytic anaemia: haemoglobin 11·7 gm. per 100 ml., red blood-cells 3·15 million per c.mm., and colour index 1·3. The marrow was megaloblastic. Free acid was present in the gastric juice; the secretion of pepsin (38 units per ml.) and the excretion of uropepsin (206 units in 24 hours) were both normal. The faeces contained no occult blood. A fat balance (four days) showed that only 85 per cent. of the daily dietary intake of 70 gm. of fat was absorbed. The daily excretion of nitrogen in the faeces was 2·7 gm., and the result of the oral glucose-tolerance test was abnormal

in that the curve was 'flattened'. A barium meal revealed the presence of a massive duodenal diverticulum, so large that it gave the appearance of a second stomach, and numerous smaller ones showing fluid levels scattered throughout the jejunum (Plate 36, Fig. 4). The pouches still contained barium when the patient was screened again four days later. Attempts to obtain a biopsy from the gastric mucosa with Wood's flexible biopsy tube proved unsuccessful. The

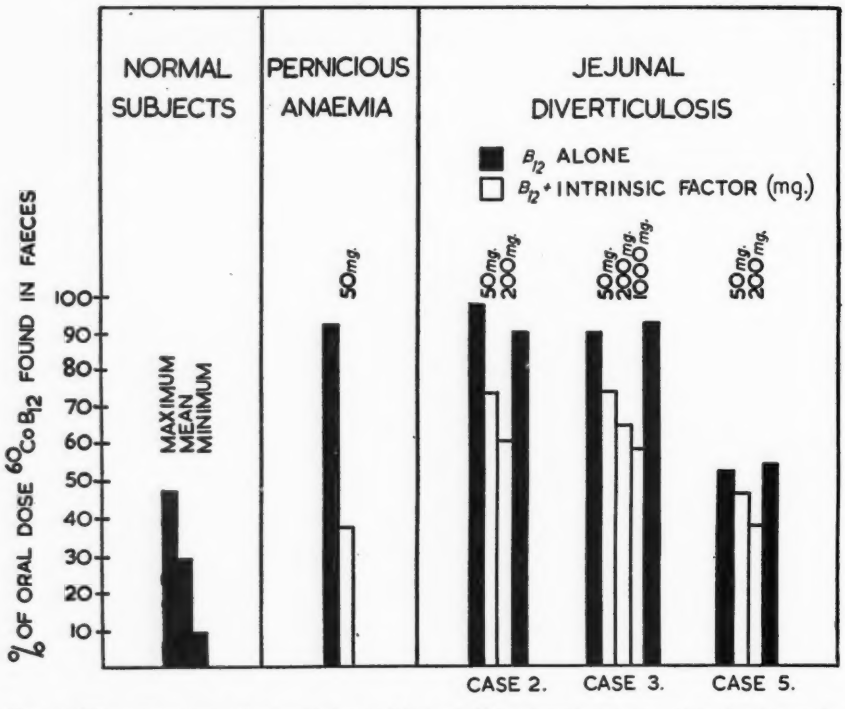

FIG. 1. The percentage of an oral dose of 0·5 μg. ^{60}Co-vitamin B_{12} found in the faeces in three patients with massive jejunal diverticulosis when the vitamin was given alone and with varying amounts of intrinsic factor.

For comparison are shown the range and mean in 30 normal subjects given vitamin B_{12} alone, and the mean in 15 patients with pernicious anaemia given vitamin B_{12} alone and vitamin B_{12}+50 mg. of the same preparation of intrinsic factor.

absorption of vitamin B_{12} was impaired (Fig. 1), over 90 per cent. of an oral dose of ^{60}Co-vitamin B_{12} being found in the faeces (normal range of excretion nine to 47 per cent. of the oral dose). The quantity of intrinsic factor effective in pernicious anaemia (50 mg.) did not increase absorption significantly, but when larger doses of intrinsic factor were given an improvement in the absorption of the labelled vitamin occurred.

She was given a high-protein, low-fat diet with added vitamins and calcium, with some relief of her symptoms. The anaemia responded to treatment with vitamin B_{12} and folic acid, but the diarrhoea proved difficult to control, and she continued to complain of abdominal pain and frequent regurgitation of food. She developed a troublesome glossitis, and continued to lose weight. Severe bouts of diarrhoea continued, and were accompanied by periodic attacks of

vomiting. A barium meal showed the stomach to be dilated and full of fluid, and the appearances suggested that the pylorus might be obstructed by an extrinsic mass. In the hope of relieving this obstruction laparotomy was performed by Mr. D. C. Corry in December 1954. At operation the upper half of the small intestine was hypertrophied and dilated. There were numerous diverticula scattered throughout its length, mostly arising from the mesenteric border. There was one very large one on the upper side of the first part of the duodenum. The other abdominal and pelvic organs appeared natural. There was no evidence of pyloric stenosis; presumably the previous pyloric obstruction had resulted from pressure from a distended duodenal diverticulum. As it appeared that nothing could be done to relieve the condition, the abdomen was closed without further surgery. Since the operation her general health has remained good, but the troublesome diarrhoea continues and has been largely uninfluenced by treatment.

Case 3 (Radcliffe Infirmary No. 171981). Housewife, aged 79 years.

This patient was fairly well until 1947 when, at the age of 72, she developed periodic attacks of colicky abdominal pain and became short of breath on exertion. These symptoms continued, and five years later, in 1952, were followed by the onset of diarrhoea, flatulence, and oedema of the ankles. Her friends noticed that she was growing pale, and she complained that her tongue was sore. She would admit to no previous illnesses. One of her sisters had died of pernicious anaemia. In August 1954 she was admitted to hospital. On examination she was pale and apathetic. She was breathless on slight exertion. For a time she was incontinent of faeces and urine. The tongue was smooth. The nails were normal. The abdomen was tympanitic, but not otherwise abnormal. There was no enlargement of the lymph-nodes.

Investigation revealed a macrocytic anaemia: haemoglobin 8·9 gm. per 100 ml., red blood-cells 2·2 million per c.mm., and colour index 1·35. The marrow was megaloblastic. A histamine test meal showed no free acid, and a greatly reduced secretion of pepsin (0·09 units per ml.; normal range 34 to 97 units per ml.). She was treated with vitamin B_{12}, 100 μg. twice weekly, and there was a rapid improvement in her general condition and in the blood count. When she was stronger further investigations were made. A barium meal revealed the presence of numerous diverticula arising from the lower end of the oesophagus, duodenal loop, and upper jejunum. A fat balance (eight days) showed that only 88 per cent. of the dietary intake of 70 gm. was being absorbed. Gastric biopsy revealed a severely atrophied mucosa, but some chief and parietal cells could be seen. The absorption of vitamin B_{12} was reduced (Fig. 1). When an oral dose of 0·5 μg. of ^{60}Co-vitamin B_{12} was given, 90 per cent. was found in the faeces, and this defect in absorption was not corrected by the addition of 50 mg. of intrinsic factor; but when very large amounts of intrinsic factor were given (1,000 mg.) absorption of the vitamin was enhanced. She has been kept under observation, and remains well apart from bouts of diarrhoea, which have resisted treatment.

Case 4 (Radcliffe Infirmary No. 203774). Housewife, aged 49 years. Transferred to the care of Professor L. J. Witts by the kindness of Dr. W. B. Matthews of Derby.

She was quite well until 1951 when, at the age of 46, she became unduly tired and began to lose weight. One year later she developed abdominal pain and diarrhoea, with fluid, evil-smelling motions. Her condition deteriorated, and in

December 1953 she was admitted to the City Hospital, Derby, under the care of Dr. Lescher. On examination she was thin and pale, with a protuberant abdomen. There were no other abnormal signs. Investigation revealed the presence of a macrocytic anaemia: haemoglobin 10·7 gm. per 100 ml., and red blood-cells 2·36 million per c.mm. The marrow was megaloblastic. Free acid was present in the gastric juice. The faeces (dry weight) contained 45·8 per cent. of fat. She was treated with vitamin B_{12}, and a partial response occurred, but improvement was more rapid when folic acid was administered. Three months later the anaemia had been corrected (haemoglobin 14·3 gm. per 100 ml., red blood-cells 5·2 million per c.mm.), but the loss of weight, abdominal pain, and diarrhoea continued in spite of a high-protein, low-fat diet with vitamin supplements.

In December 1954 the diarrhoea became worse, and she complained of paraesthesiae in the limbs with weakness of the legs. In January 1955 she was readmitted to hospital in Derby under the care of Dr. W. B. Matthews. On examination she had a high fever (temperature 104° F.), and was emaciated, but not pale. The abdomen was distended, but not tender. The most striking findings were neurological. There was severe flaccid weakness of the legs, with sensory loss of a 'stocking' distribution. The reflexes in the legs were absent, and the plantar responses were flexor. At this time the haemoglobin was 13·9 gm. per 100 ml., red blood-cells 4·7 million per c.mm., and white cells 6,200 per c.mm. Lumbar puncture showed a cerebrospinal-fluid pressure of 160 mm.; no block was demonstrated. The cerebrospinal-fluid protein was 300 mg. per 100 ml., and there were six lymphocytes per c.mm. The Wassermann reaction in the cerebrospinal fluid was negative. The total plasma-proteins were 5·9 gm. per 100 ml. (albumin 2·9 gm. per 100 ml.), and the serum-calcium 7·4 mg. per 100 ml. The oral glucose-tolerance test gave a normal result. Trypsin was present in the duodenal juice. A barium meal revealed extensive diverticulosis of the small intestine. Soon after admission to hospital the weakness in the legs increased, and she developed retention of urine and a level of sensory loss at about L 1. X-rays of the lumbar spine were normal, but as her condition was obviously becoming worse she was transferred to the Radcliffe Infirmary under the care of Professor L. J. Witts for further investigation. The changes in the cerebrospinal fluid and the neurological signs were confirmed and, as they seemed to point to a lesion at about the level of L 1, a myelogram was performed, which revealed no abnormality. She was given a high-protein, low-fat diet with added vitamins, including folic acid 10 mg. daily and vitamin B_{12} 1,000 μg. daily. The treatment brought about no improvement, and her condition deteriorated steadily. She died one week after she arrived in Oxford. Formol saline was injected into the stomach shortly after death.

At autopsy the abnormal findings were limited to the gastrointestinal and nervous systems. Macroscopically the only remarkable feature in the stomach was thinning of the wall of the body of the organ, with loss of mucosal folds. In the jejunum there were numerous diverticula, measuring from 0·5 cm. to 4 cm. in greatest dimension (Plate 37, Figs. 5 and 6). The diverticula were closely packed, situated on the mesenteric border, and extending from the duodenojejunal flexure to the upper ileum. In the root of the mesentery near the duodenal flexure were a number of pale, yellowish, enlarged lymph-nodes, up to 5 cm. in diameter. The other abdominal organs were natural. The brain was natural, but the spinal cord was irregularly wasted, and the peripheral nerves looked abnormal. Microscopy of the spinal cord revealed varying degrees of demyelination in all columns. On section the peripheral nerves also showed patchy demyelination. Histological examination of the stomach showed some

atrophy of the mucosa of the body, but the morphology of the gastric glands was normal, and inflammatory changes were absent. The jejunal diverticula had thin walls, and were lined by intact but atrophic intestinal mucosa, in which the villi were either absent or flattened and diminished in number. In the enlarged lymph-nodes the lymphoid tissue was almost completely replaced by hyaline eosinophile exudate giving a positive stain for fibrin. In this tissue were patches of necrotic lymphoid cells and scattered macrophages with foamy cytoplasm. The capsules of the nodes consisted of fibrous connective tissue containing lymphocytes. There was no evidence of tuberculosis or neoplasm, and the appearances did not resemble those seen in Whipple's disease. The nature of the changes both in the nervous system and in the abdominal lymph-nodes is uncertain. No cause for the steatorrhoea, other than the massive diverticulosis, was discovered.

In addition to the four patients who had jejunal diverticulosis, steatorrhoea, and megaloblastic anaemia, we have observed a fifth patient who has diverticulosis and steatorrhoea, but no anaemia. A summary of the case is given below.

Case 5 (Radcliffe Infirmary No. 197192). Farm labourer, aged 52 years.

He was quite well until April 1954 when, at the age of 52, he suddenly developed abdominal pain and watery diarrhoea, with up to 12 pale, foul motions each day. He complained of flatulence, and lost over one stone in weight. The diarrhoea and colic persisted, and in October 1954 he was admitted to hospital. On examination he had no fever, and his colour was good. The only abnormal physical findings were abdominal distension and slight tenderness in the epigastrium. On examination he had no anaemia (haemoglobin 14·4 gm. per 100 ml.). There was histamine-fast achlorhydria. The excretion of uropepsin was 51 units in 24 hours, at the lower limit of normal. Gastric biopsy revealed severe atrophy of the mucosa of the body of the stomach. A fat balance (four days) demonstrated that only 82 per cent. of the daily intake of 70 gm. was absorbed. The daily faecal excretion of nitrogen was 1·8 gm. The secretion of intrinsic factor was slightly impaired, 52 per cent. and 54 per cent. of the oral dose of 0·5 μg. ^{60}Co-vitamin B_{12} being recovered from the faeces, but the addition of 50 to 200 mg. of intrinsic factor to the oral dose of radioactive vitamin B_{12} produced no significant improvement in absorption (Fig. 1). A barium meal showed that the third part of the duodenum was grossly distended, and many diverticula were present in the upper part of the small intestine. He has been treated with a high-protein, low-fat diet with added vitamins, including folic acid 10 mg. daily. He feels well, but still has bouts of diarrhoea and complains of flatulence and some central abdominal pain.

Discussion

Extensive jejunal diverticulosis and steatorrhoea are both relatively uncommon conditions. Their occurrence at the same time in a group of patients gives rise to two problems. Is the association between the two conditions fortuitous, or are they related? And if they are related, how does the one cause the other? The evidence for a direct relationship between the two is strong. It is very rare for idiopathic steatorrhoea to develop for the first time late in life. In Thaysen's series of 30 patients only three developed the condition after the age of 50, and none was over 60 years of age (Thaysen, 1932). Badenoch's series

(1952) is comparable, in that of 32 patients only two were over 50 and only one over 60 years old when the illness began. One of the patients reported here was aged 46 when her symptoms began, but the ages of the others when they first became ill were 52, 58, 64, and 72 years respectively. Moreover, the course of the illness in all our patients, and in the one reported by Dick (1955), is quite different from idiopathic steatorrhoea. The onset in every case was sudden, and two of the patients (Cases 2 and 3) suffered from recurrent abdominal pain for many months before diarrhoea developed. Predominant features of the clinical course in all the patients have been abdominal pain, frequency of relapse, and difficulty of control. In contrast, patients with idiopathic steatorrhoea, once they have improved, can usually be kept in good health so long as treatment is maintained. When steatorrhoea does occur for the first time late in life, the usual causes are destruction of the pancreas or malignant disease of the bowel. In three patients in the present series these conditions, and other less common causes of steatorrhoea, have been excluded by laparotomy or autopsy; the fourth (Case 3) has been under observation for eight years, and she remains well apart from bouts of diarrhoea. The fifth patient (Case 5), who has steatorrhoea but no anaemia, has had symptoms for only a year, but investigation has revealed no cause for the steatorrhoea other than the diverticulosis. Fatty diarrhoea has been the dominant symptom in the patients in this series, and it is surprising to find that it has not been noted more often in association with diverticulosis of the small intestine. The reason for this may be that although many patients with diverticulosis have no symptoms at all, others have attracted attention with intestinal obstruction or haemorrhage, and the urgency of their condition has caused the coincident diarrhoea to be overlooked. Some of these patients may in fact have had steatorrhoea, for the typical bulky stools are seen in only a proportion of subjects in whom fat-absorption is impaired. Moreover, in some patients who show the clinical features of steatorrhoea the radiological appearance of intestinal diverticulosis may be mistaken for clumping of barium within the lumen of the bowel, and thus the association may be missed. This was the case in the first patient we studied (Case 1).

Since massive small-intestinal diverticulosis occurs in approximately 0·3 per cent. of all people over the age of 50 years, and there is no evidence whatever that steatorrhoea itself causes jejunal diverticulosis, it remains to be discussed how the diverticulosis can give rise to steatorrhoea. In two of the patients (Cases 1 and 2) there is radiological evidence that the diverticula, once filled, emptied only very slowly. In the first of these patients opaque medium was still present in the diverticula two days, and in the second four days, after a barium meal. The effect of a large number of such diverticula with their stagnant contents might well be like that of a blind loop of intestine. Bacteria would flourish within them, and infected material spill over into the lumen of the small intestine. If this occurred it would not be surprising if it resulted in impairment of function and a failure of absorption of many substances, including fat. The greater number of the diverticula are found in the proximal part of the jejunum, and Jackson and Linder (1951) have pointed out that steatorrhoea

occurs most commonly when a stagnant loop is situated in the upper intestine. There is therefore substantial evidence to support the view that the jejunal diverticulosis and the steatorrhoea are directly related, and that the diverticulosis gives rise to the failure of fat-absorption.

It is highly probable that the megaloblastic anaemia which was present in all four patients (and in Dick's patient (1955)) is an integral part of the syndrome, and that the sequence of events is jejunal diverticulosis → steatorrhoea → megaloblastic anaemia. If this is so, examples of the intermediate syndrome would be expected to occur, as in Case 5. It could be argued that these patients, all but one of whom were elderly, were suffering from Addisonian pernicious anaemia, but all the evidence is against this hypothesis. In two of them (Cases 2 and 4) free acid was present in the stomach at the time the anaemia developed, and in Case 2 the secretion of pepsin and the excretion of uropepsin were within normal limits. Moreover, in the two patients with megaloblastic anaemia in whom the absorption of radioactive vitamin B_{12} was studied (Cases 2 and 3), the findings were not compatible with the diagnosis of pernicious anaemia. In both the absorption of the vitamin was grossly impaired, but the defect was not completely corrected by the addition of the small amount of intrinsic factor (50 mg.) which is effective in pernicious anaemia. When larger amounts of intrinsic factor were given, a further improvement occurred, a response which has been observed in other sufferers from megaloblastic anaemia associated with steatorrhoea. Finally, histological examination of the mucosa of the stomach provided additional evidence that the megaloblastic anaemia was not true pernicious anaemia. In one patient (Case 4) the morphology of the gastric glands was normal, while in the other (Case 3), although atrophy of the body mucosa was severe, occasional chief and parietal cells could be seen. This is a most unusual finding in true Addisonian anaemia.

We are grateful to Professor L. J. Witts for his helpful criticism, and to our colleagues in the Departments of Pathology and Radiology for their valuable assistance. We are indebted to Miss Julie Pink for technical assistance; to Dr. E. Lester Smith, of Glaxo Ltd., for supplies of radioactive vitamin B_{12}; to Lederle Ltd. for the preparation of intrinsic factor; and to the Medical Research Council for a grant towards the cost of the present study.

Summary

1. Four patients, two of whom died, with massive diverticulosis of the small intestine together with steatorrhoea and megaloblastic anaemia, have been studied.

2. Reasons are given for the belief that the diverticulosis is the cause of both the steatorrhoea and the megaloblastic anaemia.

3. Intestinal diverticulosis should be considered as a possible cause when steatorrhoea develops for the first time late in life.

ADDENDUM

The absorption of labelled vitamin B_{12} has been measured in two of the patients with intestinal diverticulosis after they had been given aureomycin for a period of one week. In the accompanying table it can be seen that in both patients absorption of the vitamin was enhanced appreciably, whereas in a patient with pernicious anaemia, and in another with megaloblastic anaemia associated with idiopathic steatorrhoea, there was no improvement. These observations suggest that bacterial contamination of the bowel may be responsible for the failure to absorb vitamin B_{12} in patients who have megaloblastic anaemia associated with diverticulosis of the small intestine. The comparison emphasizes still further the difference between this syndrome and either Addisonian pernicious anaemia or idiopathic steatorrhoea.

Diagnosis	*Percentage of 0·5 μg. ^{60}Co–B_{12} found in faeces*	
	Before aureomycin	*After aureomycin*
Intestinal diverticulosis:		
Case 2	90%	55%
Case 3	92%	69%
Pernicious anaemia	99%	92% 99%
Idiopathic steatorrhoea with megaloblastic anaemia	91%	99%

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FIG. 2. Case 1. Post-mortem specimen showing the stomach, pancreas, spleen, duodenum, and proximal four feet of jejunum filled with formol-saline

FIG. 3. Case 1. Post-mortem specimen. Enlarged view of proximal jejunum

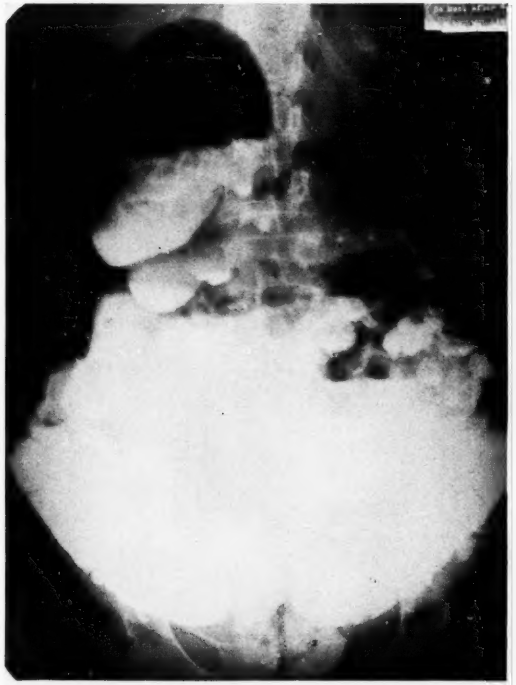

FIG. 4. Case 2. Radiograph showing the massive duodenal diverticulum, and numerous others containing fluid levels scattered throughout the small intestine

FIG. 5. Case 4. Post-mortem specimen. The upper jejunum showing numerous diverticula arising from the mesenteric border

FIG. 6. Case 4. Post-mortem specimen. View of the upper jejunum to show enlarged pale glands at the root of the mesentery

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LIVER BIOPSY IN SARCOIDOSIS[1]

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With Plates 38 to 41

The recognition of sarcoidosis is based at present on clinical and radiological appearances which together are characteristic of the disease, and on the finding of epithelioid-cell follicles in organs involved. Histological support for the diagnosis in the past has been available only when the skin or accessible lymph-nodes were affected, so that there is need for a reliable alternative. Van Beek and Haex (1943) applied needle biopsy of the liver to this purpose, and since then several small series of cases have been published. The present investigation was part of a comprehensive study of a larger series of patients with sarcoidosis. We have done liver biopsies in order to establish the frequency with which the liver is affected, and to relate such lesions to other features of the disease. We have studied the natural history of the sarcoid follicle, and the effects of treatment upon it, by means of repeated biopsies. We have also compared the follicles of sarcoidosis with those found in tuberculosis.

Patients Investigated and Methods

Ninety-three patients with sarcoidosis were investigated by liver biopsy. Thirty-one of these patients, of whom 21 had been treated with streptomycin or cortisone, had more than one test. The biopsies were compared with those taken from 69 other patients: 32 with various types of tuberculosis, 14 with pulmonary fibrosis from other causes, and 23 suffering from liver disorders and other conditions not affecting the lungs. In all, 200 liver biopsies from 160 patients have been studied. The liver has also been examined at necropsy in five cases of sarcoidosis and in 34 of tuberculosis. The diagnosis of sarcoidosis was based primarily on radiological appearances, as the disease was confined to the chest in most cases. The radiograph usually showed bilateral enlargement of the hilar lymph-nodes or symmetrical pulmonary infiltration. Beryllosis and other pneumoconioses were excluded by taking a detailed occupational history. In every patient an essential requisite for diagnosis was the absence of *M. tuberculosis* in repeated cultures of sputum or gastric washings and of the urine. Wherever possible a biopsy was done of the skin or superficial lymph-nodes for confirmation. The 93 patients with sarcoidosis were investigated during the last six years. For most of this time all new cases of sarcoidosis were investigated by liver biopsy, and were not selected for any particular reason.

[1] Received June 7, 1955.

Fifty-seven of the 93 patients were women, and 36 men. Most of them were young adults (Table I) in the third and fourth decades of life (69 in 93 cases); only three were under 21 and six over 50 years old. Thirty-four were found to have the disease on routine radiography, generally in mass miniature X-ray surveys; none of them had symptoms. Twenty-nine others complained of slight breathlessness, cough, or lassitude, for which a chest radiograph was taken.

TABLE I

Age and Sex Distribution in 93 Cases of Sarcoidosis

Age (years)	*Female*	*Male*	*Total*
Under 21	2	1	3
21–30	23	24	47
31–40	14	8	22
41–50	12	3	15
51–60	4	0	4
Over 60	2	0	2
All ages	57	36	93

TABLE II

Frequency of Organ Involvement in 93 Cases of Sarcoidosis

Hilar lymph-node enlargement and lung infiltration	39
Lung infiltration without enlarged hilar lymph-nodes	26
Hilar lymph-node enlargement without lung infiltration	25
Eyes (active or healed uveitis)	18
Splenic enlargement	13
Erythema nodosum (at onset of disease)	11
Lymph-node enlargement (biopsy control)	9
Skin sarcoids (biopsy control)	8
Digital bone lesions	6
Parotitis	2
Palate, thyroid, renal stones	each 1

Eleven patients first came under observation for erythema nodosum, five others because of cutaneous sarcoid lesions, and 10 for iritis. Two were found to have enlarged lymph-nodes on a routine examination, one complained of enlarged inguinal nodes, and one was found to have sarcoidosis following parotitis. Chronic productive cough occurred in only three patients, as a late complication of pulmonary fibrosis. Abnormal physical signs in the lungs were usually absent in the early stages of the disease, even with widespread miliary infiltration, though coarse crepitations were present in the late fibrotic stage. Uveitis, splenic and lymph-node enlargement, and skin sarcoids were the only other features of the disease commonly seen. Table II shows the distribution of the lesions in the 93 patients. Tuberculin sensitivity was usually low or absent.

Liver biopsy was done by a modification (Terry, 1949) of the technique described by Gillman and Gillman (1945). Details are given in the Appendix. This method has several advantages: it is safer because of the short time the needle is kept in the liver, it produces unfragmented tissue of adequate size, and failure to get a specimen is less frequent than with other methods. Thus only 10 of our 200 biopsies were unsuccessful, compared with 22·5 per cent. (Iversen and Roholm, 1939) and 40 per cent. (Greene, 1944) by other tech-

niques. Complications were unusual, there being no fatalities, and no examples of peritonitis or of haemorrhage requiring transfusion. One patient had a small haemothorax requiring aspiration, and approximately 5 per cent. of the patients suffered pain for several hours, which was usually referred to the right shoulder, and was probably due to a small haemorrhage beneath the diaphragm. Only two planned biopsies had to be abandoned, one because the patient was extremely nervous, and the other because a severe reaction followed the introduction of local anaesthetic. Most patients complained of only slight discomfort, so that requests for repeated biopsies were readily granted. Fifty serial sections were examined from each specimen, to increase the area available for scrutiny and to allow doubtful collections of cells to be traced through several sections. Often these proved to be portal tracts cut obliquely and surrounded by a few lymphocytes and fibroblasts, but sometimes they were clearly the cut edges of typical 'sarcoid' follicles. Our criteria for accepting a lesion as a sarcoid follicle were: (1) it should have a minimum diameter of 50μ, since the significance of smaller collections of cells is uncertain; (2) the predominant cell should be reticulo-endothelial ('epithelioid'); the presence of giant cells and lymphocytes, though common, was not considered essential; and (3) the lesion should be traceable through serial sections to exclude artefacts.

Results

Clinical. Epithelioid-cell follicles were found in 59 (63 per cent.) of the 93 patients who were thought to have sarcoidosis on clinical and radiological grounds (Table III). There was no significant difference, as regards the frequency with which follicles were found, between patients who had diffuse pulmonary disease, with or without enlarged hilar lymph-nodes (40 in 65 cases), and those who had enlarged hilar nodes only (18 in 25 cases). Hepatic sarcoidosis, however, was more common in those who had enlarged hilar nodes together with widespread pulmonary infiltration (30 in 39 cases) than in those who had pulmonary disease alone (10 in 26 cases). Fourteen of the 18 patients with active or healed uveitis, nine of the 13 with splenic enlargement, and seven of the nine with peripheral lymph-node enlargement had sarcoid lesions in the liver.

TABLE III

Clinical Extent of Sarcoidosis related to the presence of Hepatic Follicles

Type of disease	*Number of patients*	*Number with follicles in liver*
Hilar lymph-nodes and lung infiltration	39	30
Lung infiltration only	26	10
Hilar lymph-nodes only	25	18
Uveitis (active or healed)	18	14
Splenic enlargement	13	9
Erythema nodosum (recent)	11	10
Lymph-node enlargement	9	7
Skin sarcoids	8	3
Total cases of sarcoidosis	93	59 (63%)

Ten of the 11 patients with erythema nodosum together with hilar-node or lung involvement had epithelioid-cell follicles in the liver, but only three of the eight with typical skin sarcoids. Table IV shows the findings in the liver biopsies analysed according to the tuberculin sensitivity of the patients. Fourteen out of 23 patients who had a positive reaction to 10 tuberculin units (t.u.), and 18 out of 26 patients who had a positive reaction to 100 t.u., showed sarcoid follicles in the liver. A comparable proportion (27 out of 44) of those who gave no

TABLE IV

Relation of Mantoux Reaction to the presence of Hepatic Sarcoidosis

Liver histology	*Mantoux reaction*		
	positive		*negative*
	1:1,000 (10 t.u.)	*1:100 (100 t.u.)*	*1:100 (100 t.u.)*
Follicles present . . .	14	18	27
Follicles absent . . .	9	8	17
Total	23	26	44

reaction to 100 t.u. had similar lesions. There was thus no relation between the degree of tuberculin sensitivity and the presence or absence of sarcoid follicles in the liver. Because symptoms were indefinite, the duration of the disease prior to investigation and liver biopsy could be estimated only approximately, but in 36 cases it was thought to be less than a year. Sometimes a biopsy was taken within a month of the onset of iritis or erythema nodosum; on the other hand some patients were already known to have had their disease for a long time, the longest time being 25 years. When the disease had been present for several years there was frequently hyaline fibrosis within or around the follicles. Apart from this it was not possible to judge the age of the disease from the histological appearance. Whenever possible the diagnosis was confirmed by biopsy of tissues other than the liver. Biopsies of skin, lymph-nodes, or lung showed sarcoid follicles in 20 instances, and a necropsy confirmed the diagnosis subsequently in one other patient. Thirteen of these 21 patients showed typical follicles in the liver. Thus the frequency of hepatic lesions was similar whether or not there were confirmatory biopsies. The histological proof of sarcoidosis rested on the liver biopsy alone in 47 patients, or half the group. Histological confirmation was not obtained from any source in 25 of the whole group.

Liver function was investigated in order to determine whether the presence of sarcoid follicles in the liver was accompanied by any detectable derangement of function. There was no clinical evidence of this, such as jaundice or enlargement of the liver, except in one instance in which congestive cardiac failure had supervened. The prothrombin time was estimated before each biopsy, and on one occasion only was it abnormally prolonged so that the biopsy was postponed. Differential protein analyses by the micro-Kjeldahl method showed no disturbance of the serum-albumin fraction. A serum-globulin level of over 3 gm. per 100 ml. was found in only 10 of the 93 patients; six of these had sarcoid

follicles in the liver; four did not. Two patients with globulin levels of over 4 gm. per 100 ml. had extensive sarcoidosis of long duration, but apart from these there was no relation between the extent or duration of disease and hyperglobulinaemia. In three instances of extensive sarcoidosis the globulin levels were abnormally low (1·04 gm., 0·77 gm., and 0·64 gm. per 100 ml.). One of these patients had numerous follicles in the liver, but the other two yielded normal biopsy specimens. For comparison a differential protein analysis was done in 14 patients with active pulmonary tuberculosis; two of them had increased serum-globulins. Twenty-four patients had tests of thymol, zinc-sulphate (Kunkel), and ammonium-sulphate turbidity. The results were normal in 20 of these patients, of whom 15 had follicles in the liver; they were abnormal in the remaining four, all of whom showed typical lesions in the liver. One of these patients had a zinc-sulphate turbidity of 7 units and ammonium-sulphate turbidity of 6 units; two others had abnormal zinc-sulphate turbidities only (6 and 7 units), and the other had a thymol turbidity of 10 units. The normal results for these tests are less than 4 units, and high figures usually indicate disproportion of the serum-proteins. In none of the four patients with an abnormal serum turbidity, however, was the level of albumin or globulin altered.

Bacteriology. Sections of liver from 12 patients were stained by Ziehl-Neelsen's method, but no acid-fast bacilli were seen. Portions of the biopsy specimen from 26 patients were examined by culture on Löwenstein's medium, and macerated samples of liver from 28 patients were inoculated into guinea-pigs. *M. tuberculosis* was never isolated. Since these tests were made before microscopic examination, about half the specimens were subsequently shown to have no sarcoid follicles in the liver. As controls we made 10 cultures and nine guinea-pig inoculations of liver-biopsy material from patients with active tuberculosis, including two with miliary disease involving the liver; these also gave negative results.

Histology. The size of the biopsy specimen obtained from the liver was variable. In 10 instances none was obtained on the first attempt, in 11 the length was less than 5 mm., and in 18 between 5 and 10 mm., whereas 10 specimens measured 20 mm. or more. The average size of the mounted sections was 11·87 $\times$1·5 mm., which is of course smaller than the fresh tissue because of shrinkage in fixation. The diameter remained fairly constant owing to the internal bore of the biopsy needle. The average length of the specimen when no lesions were found was 10·5 mm., slightly but not significantly smaller than the average of 11·87 mm. for the series. Error in detecting the presence of sarcoid follicles due to an inadequate sample is thus not likely to have been an important source of negative results. The number of follicles in each biopsy varied greatly. Care was taken to avoid counting a lesion more than once in serial sections. The density of follicles varied from 25 in a specimen 12 mm. long to only one in a strip of liver 22 mm. in length. The average specimen represented one 50,000th part of the liver, and contained three follicles. The size of the individual lesion varied greatly (Plate 38, Figs. 2*a* and 3*a*); the minimum size for acceptance was 50μ, and the maximum diameter of the largest was 1,000μ. The

average size, measured across the greatest diameter, was 240μ. The size of the lesions in any one specimen was fairly constant, but there were some examples of great differences. The site of the follicle in the liver lobule varied; in particular there was no constant association with portal tracts, and many small follicles occurred in the mid-zone. Most follicles were clearly demarcated from the liver parenchyma. The smaller follicles were spherical, but many of those larger than 400μ were lobulated, as though they might have been formed by aggregation of smaller ones (Plate 38, Fig. 3*a*).

The cellular content of the follicles was remarkably constant, reticulo-endothelial (epithelioid) cells forming from one-half to nine-tenths of all the follicles. The numbers of lymphocytes varied; they usually formed a thin rim round the periphery together with a few fibroblasts. Eosinophile cells and plasma cells were rare. Multinucleated giant cells were present in three-quarters of the follicles, but only in small numbers in most of them. Their size and shape were inconstant; some had peripheral nuclei, as seen frequently in tuberculosis, others had nuclei scattered at random throughout the cytoplasm. Asteroid inclusion bodies (Plate 39, Fig. 4) were found in only four biopsies, and typical Schaumann inclusions were not seen. Necrosis was not found, but a small area of hyaline or granular material devoid of nuclei was seen in the centre of lesions from three patients. Stains for reticulin (Plate 39, Figs. 5*a*, 5*b*) showed an incomplete network surrounding the epithelioid cells, and a denser condensation of reticulin around the periphery of the follicles. Bands of fibrous tissue, with characteristic staining reactions, were found in or around the follicles of six specimens only (Plate 40, Fig. 7*a*), all, with one exception, from patients with sarcoidosis of several years' duration. By contrast, three patients known to have had sarcoidosis for several years had follicles without fibrosis. Except for the presence of fibrosis in disease of long standing, the density, size, or cellular content of the follicles could not be related to the duration or clinical extent of the disease. The liver parenchyma was abnormal in only nine patients; they showed fatty changes, and were obese or had been in bed for some time. Four others, in whom no follicles were found, had lymphocytic aggregates in the portal tracts, an appearance which is found in other diseases and is not peculiar to sarcoidosis.

Evolution of the hepatic follicle. In order to study the natural history of the liver lesion, repeated biopsies were taken from 10 patients. In two the specimens were repeatedly normal, in spite of typical clinical and radiological features of sarcoidosis. In three, whose pulmonary disease remained and even increased in density, epithelioid-cell follicles persisted unchanged even after four years. Two others, in whom the liver had originally contained typical follicles, had a spontaneous resolution of the disease as judged by radiographs; specimens of adequate size taken seven months later were normal, and contained no scars. On the other hand three patients had persisting lesions in spite of the complete disappearance of radiographic abnormalities; in one the follicles were fewer and smaller, and contained a predominance of lymphocytes and fibroblasts, 12 months after the original biopsy; in the other two the follicles were several times

larger, four and 16 months later respectively (Plate 38, Figs. 2*a* and 2*b*). Some of these follicles were lobulated in outline, as though they had been formed by the aggregation of small follicles; they contained more giant cells and hyaline material. One of these patients had a third biopsy one year later, when no abnormality was seen.

Streptomycin and p-*aminosalicylate treatment.* As we have already reported (Hoyle, Dawson, and Mather, 1955), selected patients from the present series were treated with antituberculous drugs, and others with cortisone in addition. Twelve patients who were treated with streptomycin and sodium aminosalicylate (PAS) had serial liver biopsies. In two the histological appearances were normal both before and after treatment. Two of the remaining 10 patients showed no change in their hepatic follicles after three months' daily treatment; their chest radiographs also remained unchanged. Three patients who improved radiologically showed fewer but larger follicles in biopsies after seven months of treatment. Each lesion contained larger numbers of giant cells, and frequently abundant hyaline material. Serial biopsies from two patients who responded to treatment showed increasing fibrosis within and around the lesions, as well as diminished size and cellularity (Plate 38, Figs. 3*a* and 3*b*). Two patients showed disappearance of sarcoid follicles after seven months of treatment with streptomycin and PAS, during which the disease elsewhere also improved.

Cortisone and streptomycin treatment. This form of treatment was used only for severe or progressive forms of the disease, usually after many years of observation, and often after streptomycin had already failed to give improvement. Serial biopsies were taken from nine patients so treated. All the patients showed a pronounced improvement clinically and radiographically, although all except one relapsed when treatment was stopped. In three, in spite of sarcoidosis of over two years' duration, the follicles in the liver completely disappeared. A third biopsy from one of these three patients, who was known to have had the disease for 12 years, was still normal one year after treatment was stopped; conjunctival biopsies from another patient showed a parallel resolution of sarcoid follicles. In three other patients the lesions diminished greatly in number and size, but fibrous tissue remained (Plates 39 and 40, Figs. 5, 6, and 7). In the remaining three the follicles were fewer but not smaller, and again there was an apparent increase of fibrosis.

Hepatic follicles in tuberculosis. Biopsies were taken from 32 patients with tuberculosis (Table V). Three patients with miliary tuberculosis, and four out of 10 with active primary tuberculosis, had follicles in the liver. In contrast, follicles were seen only once in 19 patients with other forms of the disease. Fifteen of these had active phthisis with tubercle bacilli in the sputum, two were examples of fibroid tuberculosis, and two of non-pulmonary tuberculosis. None had previously received streptomycin. The liver biopsies from the three patients with miliary tuberculosis and the four with primary disease, and from one patient who had extensive pulmonary tuberculosis, contained follicles indistinguishable from those found in sarcoidosis (Plate 41, Figs. 8 and 9). There was no necrosis, and tubercle bacilli were not demonstrable. There were

rather more lymphocytes in the periphery of some follicles than is usual in sarcoidosis, but there were many examples with an identical cellular content. Our observations show that there are no clear histological differences between the hepatic follicles found in sarcoidosis and those found in tuberculosis before caseous necrosis has occurred. Necropsy specimens of liver from 34 cases of tuberculosis were examined (Table V). The average size of the cut section was

TABLE V

Hepatic Follicles in Tuberculosis

		Biopsy	*Necropsy*
Primary disease	Number of patients	10	0
	Follicles present in	4	0
Miliary and meningeal	Number of patients	3	19
	Follicles present in	3	12
Pulmonary and other types	Number of patients	19	15
	Follicles present in	1	0

TABLE VI

Hepatic Follicles in Erythema Nodosum

Probable cause	*Number of patients*	*Liver follicles present*	*Chest radiograph*	*Tuberculin reaction*	*Recent sore throat*
Sarcoidosis	11	10	Bilateral hilar nodes (10)	2 positive 1:1,000	0
			Bilateral lung infiltration (5)	4 positive 1:100	
				5 negative 1:100	
Tuberculosis	4	1	Primary complex (3)	All positive 1:10,000	0
			Apical focus (1)		
Streptococcal infection	5	0	Normal	3 positive 1:10,000	4
				2 negative 1:1,000	

14×16 mm., so that an area of liver was examined equivalent to the serial sections of an average biopsy specimen. Nineteen patients had died of miliary or meningeal disease: 12 of these had follicles in the liver, which were necrotic in 11. In one of these patients, who had had prolonged streptomycin treatment, most of the lesions were fibrotic. One patient, a child aged 11 months who died of acute miliary tuberculosis and bronchopneumonia, showed only non-caseating follicles indistinguishable from sarcoid lesions. None of five patients who died of pulmonary tuberculosis showed any active or healed granulomatous lesions in the liver. Two of these had received prolonged treatment with streptomycin. More significant were the findings in 10 patients who died of unrelated diseases, but in whom there were active caseating lesions in the lung (nine) or in the kidney (one). Careful scrutiny of sections of the liver revealed no structures resembling tubercle follicles in any of them.

Erythema nodosum. Liver biopsies were taken from 20 patients with recent erythema nodosum (Table VI). Eleven patients had enlarged hilar nodes or bilateral pulmonary infiltration due to sarcoidosis, and are included in the results given above (Table III); ten had follicles in the liver indistinguishable from the other cases of sarcoidosis. Four patients had tuberculosis with a primary

complex in the lung: follicular structures in the liver, similar to those found in sarcoidosis, were seen in one of them. Five patients gave a history of recent throat infections, and had normal chest radiographs; although the organisms were not isolated, the eruption was presumed to be a sequel of streptococcal infection. Liver biopsies were normal in each instance.

Miscellaneous diseases. There were 32 other control subjects. One group of 14 patients suffered from various pulmonary fibroses: pneumoconiosis (four), chronic bronchopulmonary infection with fibrosis (four), pulmonary fibrosis of unknown cause, with no evidence of tuberculosis or sarcoidosis (four), scleroderma of the lung (one), and eosinophilic xanthomatous granuloma (one). No follicles were found in any of the biopsies from these patients. Similarly no follicular structures could be found in the biopsies from 18 patients with non-pulmonary disease such as hepatic cirrhosis (12) and brucellosis (two). One of the two patients with brucellosis had recurrent febrile episodes, shown to be due to brucella infection by blood culture and a high titre of specific agglutinins; the other had chronic brucella meningitis, shown by a rising titre of agglutinins and a positive brucellin test.

Discussion

Sarcoidosis when confined to the lungs may easily be confused with other causes of widespread pulmonary infiltration or fibrosis, and when the hilar lymph-nodes alone are affected the reticuloses need to be excluded. Its recognition is important also because ocular and severe pulmonary sarcoidosis may require treatment. In the past various features, which were thought to be peculiar to sarcoidosis, were used to support the clinical diagnosis. In particular a negative Mantoux test was regarded as obligatory. Recently, however, Löfgren (1953) found that some sensitivity to tuberculin was common in sarcoidosis. We have confirmed this observation by showing a similar frequency of follicles in the liver among patients with and without tuberculin sensitivity (Hoyle, Dawson, and Mather, 1954; and Table IV). Sometimes a raised level of serum-globulin, or the presence of digital bone lesions, has been relied upon for diagnosis. But in the present series only 10 of the 93 patients had hyperglobulinaemia, and only six had digital bone lesions. Histological confirmation is equally limited if skin sarcoids or enlarged superficial lymph-nodes, the main sources in the past, are relied upon. These were available on only 17 occasions in the present series of 93 patients. Gormsen (1948) had little more success by examining the bone-marrow, for among 39 patients with sarcoidosis he found typical epithelioid-cell follicles in 10 only. The Kveim test has been little used in this country, but has been reported upon favourably by James and Thomson (1955). The disadvantages seem to be the need to prepare a special agent and the delayed result.

Liver biopsy was first used as an aid in the diagnosis of sarcoidosis by van Beek and Haex in 1943. They found epithelioid-cell follicles in two of four patients. Van Buchem (1946) found 11 positive biopsies in 14 patients, but gave few clinical or histological details. The first careful inquiry into the value

of liver biopsy was made by Klatskin and Yesner (1950) who found typical epithelioid-cell follicles in 15 of their 20 patients. The liver gave the only histological confirmation of the diagnosis in 12. The only other important series of biopsies was reported by Shay, Berk, Sones, Aegerter, Weston, and Adams

TABLE VII

Liver Biopsy in Sarcoidosis

Author	*Number of cases*	*Number with sarcoid follicles*	*Comment*
Cameron and Dawson (1942)	1	1	Surgical biopsy
van Beek and Haex (1943)	4	2	One case doubtful
van Buchem (1946)	14	11	5 doubtful (poor description). 3 ? tuberculosis
Volwiler and Jones (1947)	2	2	No clinical or histological details given
Scadding and Sherlock (1948)	4	4	Case 1 probably normal liver; Case 4 a coincidental finding
Klatskin and Yesner (1950)	20	15	
Scadding (1950)	4	2	
Baird, Bogoch, and Fenwick (1950)	3	3	
Shay, Berk, Sones, Aegerter, Weston, and Adams (1951)	21	16	Plus one doubtful biopsy
Moyer and Wurl (1951)	6	5	
Longcope and Freiman (1952)	8	5	2 surgical biopsies
Dolphin and Heathfield (1952)	1	1	
Dagradi, Sollod, and Friedlander (1952)	1	1	
Finckh, Baker, and Ryan (1953)	3	3	
Total	92	71 (77%)	
Present series (1955)	93	59 (63%)	

TABLE VIII

Liver Necropsy in Sarcoidosis

Author	*Number of necropsies in which liver was examined*	*Number with sarcoid follicles*
Lenartowicz and Rothfeld (1930)	1	0
Garland and Thomson (1933)	3	1
Snapper and Pompen (1938)	1	1
Friedman (1944)	1	1
Rubin and Pinner (1944) (includes 18 from literature)	36	22
Granström, Gripwall, Kristofferson, and Lindgren (1946–7)	2	1
Ricker and Clark (1949)	22	18
Longcope and Freiman (1952)	27	14
Present series (1955)	5	1
Total	98	59 (60%)

(1951), who found positive biopsies in 16 out of 21 patients, but did not state their criteria for diagnosis, nor did they make serial sections. These and other reports of liver biopsy in sarcoidosis are summarized in Table VII. The total of 71 positive results in 92 cases may be erroneously high, because serial sections

were not always made (so that normal portal tracts cut tangentially could have been falsely interpreted), and also because of the natural tendency to report positive findings. This criticism is supported by the findings in 98 necropsies (Table VIII) and by the results of the present investigation, which both show a lower incidence of follicles in the liver. Our results with liver biopsy show that it is of greater value in demonstrating the follicles than any alternative means. Follicles were found in about three-fifths of the 93 patients, a similar frequency to that found at necropsy. Furthermore, liver biopsy provided the sole means of confirming the diagnosis in 47 of the 93 patients.

Although the value of liver biopsy in sarcoidosis is thus established, it is necessary to consider its safety before it can be advocated as a method of choice for general use. When Terry analysed the complications of over 10,000 biopsies in 1952, he found that the mortality was 0·12 per cent., and the incidence of major complications, principally haemorrhage or biliary peritonitis, 0·32 per cent. His analysis dealt with biopsies done on patients with a wide variety of hepatic disorders, and most mishaps occurred in patients who were severely ill or deeply jaundiced, or where there was inadequate preparation or an inexperienced operator. Patients with sarcoidosis are seldom ill, and jaundice is extremely rare (Branson and Park, 1954). The procedure should be undertaken only when the patient is in hospital, and after careful clinical and haematological examination (see Appendix). Provided these precautions are taken, the risks are extremely small, and comparable with those of many routine diagnostic procedures. In the present investigation 200 biopsies were performed, and there were no deaths and no serious complications.

One possible limitation to the usefulness of liver biopsy is that the specimen may be inadequate. Though follicles are sometimes seen in small specimens, a strip of liver 10 mm. long or more is desirable. Even then there are sampling errors in the method, and it is never possible to state that there are no hepatic lesions from the results of needle biopsy. Yet these errors must be small, as there is a close similarity in the frequency of lesions seen at biopsy and at necropsy (Tables VII and VIII). Furthermore, when biopsies were repeated in our series, hepatic follicles were always found when the specimen was of adequate size and when the disease persisted elsewhere. On the other hand, when an original specimen did not contain follicles, later biopsies failed to show them. We conclude that needle biopsy gives an accurate index of liver involvement, which amply justifies its use.

The frequency of hepatic sarcoid follicles in relation to clinical affection of other organs was remarkable only in regard to the lungs and to erythema nodosum (Table III). The follicles were found in the liver as frequently in patients with bilateral enlargement of the hilar lymph-nodes as in those with pulmonary sarcoidosis. This fact is further evidence that bilateral enlargement of the hilar nodes is usually a manifestation of sarcoidosis, confirming the views of Löfgren (1953). On the other hand the follicles were found more commonly in the liver when pulmonary sarcoidosis occurred together with hilar-node enlargement (30 out of 39 patients) than when pulmonary sarcoidosis only was present (10 out

of 26 patients). The different frequency of hepatic follicles in these two groups of patients was probably due to the inclusion in the latter group of several cases in which the pulmonary lesions were fibrotic rather than cellular. Necropsy studies in two of our patients support this contention, in that there was extensive pulmonary fibrosis with no recognizable sarcoid follicles in the lung or other tissues, although the lesions had previously been found in biopsy specimens.

Although hepatic follicles are common in sarcoidosis, the liver is seldom enlarged except from terminal congestion with heart failure. Jaundice is also extremely rare (Ross and Weinberg, 1951; Branson and Park, 1954). Hyperglobulinaemia and increased alkaline phosphatase have, however, been reported frequently since their recognition in sarcoidosis by Harrell and Fisher in 1939. These workers found the serum-globulin level above 3·0 gm. per 100 ml. in nine out of 11 patients, and Longcope and Freiman (1952) in 44 out of 107 patients. The abnormality has been shown to be due to an increase of the γ-globulin fraction at the expense of the albumin (Fisher and Davis, 1942; Seibert and Nelson, 1942, 1943; Shay, Berk, Sones, Aegerter, Weston, and Adams, 1951). Shay also found abnormal results of zinc-sulphate and thymol turbidity tests in a high proportion of cases (21 in 24 and 13 in 24 respectively), but only in cases of active sarcoidosis, and not in those with predominant fibrosis. The electrophoretic pattern was similar to that associated with the formation of antibodies in response to known infections. Studies of liver function in the present series showed an increased serum-globulin in only 10 out of 93 patients, and an abnormally low level in three patients. Electrophoresis was not available, but turbidity tests, which reflect disproportion of the proteins, were abnormal in only four of 24 patients tested. It was not possible to relate the abnormal results to the extent of hepatic sarcoidosis as judged by liver biopsy, a result which is in accord with the findings of Klatskin and Yesner (1950) and Shay, Berk, Sones, Aegerter, Weston, and Adams (1951). The frequency of hyperglobulinaemia was much less than that usually reported. Although many of our patients had predominant pulmonary disease, and only a small proportion had splenic and lymph-node enlargement, the liver was affected histologically as frequently as in most other series, nor was there any evidence that hyperglobulinaemia was prone to occur when splenic or lymph-node enlargement was present. The explanation may be that most of our patients were less severely ill than some of those encountered in North America. An increase of serum-globulins is found in many other diseases, among them tuberculosis (Eichelberger and McCluskey, 1927; Hurst, Maier, and Lough, 1947); Seife, Kessler, Hoffman, and Lisa (1951) found it in 54 out of 70 subjects. Determination of serum-proteins is therefore valueless in the diagnosis of sarcoidosis and in its differentiation from tuberculosis. The cause of hyperglobulinaemia is still obscure, but when it occurs in these diseases it may be related to widespread stimulation of the reticulo-endothelial system.

Evolution of the follicles and the effect of treatment. Though repeated needle biopsies have often been used to study diffuse diseases of the liver, such as hepatitis, they have not so far been used in sarcoidosis. The liver is most suit-

able for studying the development of sarcoid lesions, as it is seldom possible to obtain material repeatedly from other sites for comparative histology. It is valid to compare the changes in one specimen with those seen in a later biopsy, as the lesions in any one section are similar in size and structure, and are presumably representative of the changes throughout the liver. This method can therefore be used to compare the histological with the clinical progress of the disease. When the disease persisted in the lungs, two successive liver biopsies both contained follicles; the later one usually showed little structural alteration, even when taken after an interval of several years. Thus the lesions can remain cellular in the liver for long periods, though insidious fibrosis may be occurring in the lung. No examples of diffuse hepatic fibrosis were seen, presumably because the tissue reaction in the liver differs from that in the lung. When the disease resolved, either spontaneously or during treatment with streptomycin and PAS, the follicles either disappeared or became smaller and fewer with an apparent increase of fibrous tissue. Occasionally they became bigger and showed increased numbers of giant cells and hyaline material. This enlargement may be the last stage before disappearance of the follicles, as it occurred at a time when the radiograph had just returned to normal. Lesions in the lung, however, were probably still present, although too few to be visible radiographically. This circumstance has a parallel in miliary tuberculosis, in which Janbon, Cazal, and Bertrand (1949) noted that the radiograph became normal before the tuberculous follicles disappeared from the liver.

The histological changes during streptomycin treatment did not differ much from those seen during natural remission. The effect of cortisone in conjunction with streptomycin and *p*-aminosalicylate on the follicles was more striking. In three instances there was complete disappearance of the follicles, in three others diminution in their number and size with increased fibrosis, and in the remaining three the follicles were slightly larger and more fibrotic, but less numerous. There was improvement in the radiographs of all nine patients: one cleared completely, and the others only partially, probably because in these there was too much fibrosis to allow complete radiological clearing. Clinical remission occurred in every case, as judged by the healing of skin and eye lesions and diminution of splenic enlargement. There is thus little doubt of the effectiveness of cortisone in sarcoidosis, although the disease relapses when treatment ends. Serial liver biopsies show that improvement is often associated with actual disappearance of cells from the follicles. Any apparent increase of fibrous tissue is due to its condensation rather than to any new formation (Plates 39 and 40, Figs. 5, 6, 7). Presumably the same process occurs in the lungs, so that absorption of cellular lesions would appear to be the chief cause of radiological clearing. Where there is already much fibrosis, as in pulmonary sarcoidosis of long duration, the beneficial effect is slight. It is thus logical to give cortisone treatment early in the disease if there is no spontaneous resolution, as inhibition of the cellular reaction may prevent progressive fibrosis in the lungs, eyes, and other organs. Serial liver biopsies seem to offer an additional method of assessing the effect of any new agent that may be used in the treatment of sarcoidosis.

Hepatic follicles in other diseases. It is important to know how often epithelioid-cell follicles are found in the liver in other diseases, and whether they differ from those seen in sarcoidosis. They are said to be present in brucellosis (Cazal, 1949; Spink, Hoffbauer, Walker, and Green, 1949; Barrett and Rickards, 1953), chronic berylliosis (Martland, Brodkin, and Martland, 1948; Chesner, 1950; Hardy, 1951), and histoplasmosis (Pinkerton and Iverson, 1952). These authors

TABLE IX

Liver Biopsy in Tuberculosis: Frequency of Tubercle Follicles

	Miliary tuberculosis		*Primary tuberculosis*		*Pulmonary and other forms*		
Author	*Number of cases*	*Biopsy positive*	*Number of cases*	*Biopsy positive*	*Number of cases*	*Biopsy positive*	*Comment*
Olivet (1926) . .	..	..	..	..	15	0	Fatty degeneration or amyloid found in 8 cases
van Buchem (1946) .	..	..	..	..	9	0	No clinical or histological details
van Beek and Haex (1948)	..	..	10	7	..	..	4 may have been sarcoids
Janbon, Cazal, and Bertrand (1949)	24*	?	..	..	..	..	State that follicles were found in cases of spread by bloodstream, but in only 2 cases showing cavities and positive sputum
van Beek, Haex, and Smit (1949)	1	1	3	3	3	3	Numerous minute lesions accepted. All biopsies reported showed follicles; not stated whether other biopsies were done
Klatskin and Yesner (1950)	4	4	1	1	12	2	1 pulmonary case probably sarcoidosis
Seife, Kessler, Hoffman, and Lisa (1951)	..	..	..	..	70	9	Tubercles were caseous. Also reported acute focal necroses in 50 cases
Finckh, Baker, and Ryan (1953)	5	5	1	1	24	1	The 'primary tuberculosis' was a pleural effusion; the case was called miliary by the authors on the basis of biopsy
Present series . .	3	3	10	4	19	1	
Total . . .	13	13	25	16	152	16	

* Excluded from total, as number of positive biopsies not given.

have stated that the appearances of liver lesions in the conditions which they describe can be identical with those seen in sarcoidosis. We have no evidence on this point, but fortunately the affections referred to are rare in this country, and have distinctive features which make their separation easy. Epithelioid-cell follicles may also occur with erythema nodosum, and van Beek and Haex (1948) and Klatskin and Yesner (1950) have emphasized this association. In our experience the presence of lesions in the liver depends upon the cause of the eruption. They are found frequently when erythema nodosum is associated with sarcoidosis (10 in 11 cases); they are also found when it is due to primary tuberculosis (one in four cases), but not when the eruption follows streptococcal infection (Table VI).

Apart from sarcoidosis, tuberculosis is the condition which most commonly produces epithelioid-cell follicles in the liver. When caseation has occurred they can be easily distinguished from those seen in sarcoidosis. Nickerson (1937) considered that tubercle follicles could be identified, even without necrosis, by the presence of typical Langhans giant cells, and by their position in the midzone of the liver lobules. This view was not confirmed by Klatskin and Yesner

TABLE X

Necropsies in Tuberculosis: Frequency of Tubercle Follicles in Liver

Author	*Number of cases*	*Number with follicles*	*Comment*
Ullom (1909)	100	79	Majority of cases had intestinal ulceration
Lavenson and Karsner (1909–10)	50	19	15 of the positive cases had miliary or abdominal disease. In only 4 out of 19 instances of pulmonary tuberculosis were follicles found
Lorentz (1913)	100	99	Not stated whether terminal miliary spread occurred
Torrey (1916)	131	82	33 had overt miliary, and many others abdominal tuberculosis. No follicles found in liver in 29 instances of patients with active tuberculosis who died of unrelated causes
Saphir (1929)	100	80	Not stated whether patients died of terminal miliary disease. 57 patients had tuberculous ulcers of intestines
Present series (1955)	34	12	12 positive cases were in miliary or meningeal tuberculosis. No follicles in 10 patients with active pulmonary disease who died of unrelated causes, or 5 patients who died of that condition

(1950), nor do our own observations support it. Asteroid and other giant-cell inclusions have no diagnostic value, as they are rare and not peculiar to sarcoidosis (Wolbach, 1911; Jaques, 1952). Hamperl (1953) reported the presence of small groups of cells (*Retothelknötchen*) in one-quarter of a series of patients with tuberculosis. We have not seen any such collections of cells which could be considered abnormal in either tuberculosis or sarcoidosis. Cultures and animal inoculations of liver tissue do not differentiate tuberculosis from sarcoidosis, as it is always difficult to isolate *M. tuberculosis* from small portions of tissue. In our experience it is not possible to distinguish the lesions in the liver of the two diseases unless caseation is present. The follicles which are found in tuberculosis do not occur with equal frequency in its different forms (Table IX). They are seen most commonly in miliary disease, both in biopsies and at necropsy (Table X). This remark applies whether the miliary spread follows primary infection or is the last event in the course of adult forms of the disease, especially extensive abdominal tuberculosis (Parini, 1941). In these circumstances casea-

tion is always present, except in the less acute forms of miliary disease, as we have observed on three occasions (Plate 41, Fig. 8). By contrast, follicles are not usually seen in the liver in the ordinary adult forms of pulmonary tuberculosis; we were able to find them only once in biopsies from 19 patients, all of whom had extensive disease. Records of 152 cases investigated in this way (Table IX) show that the liver was affected in only 16. Earlier studies by Torrey (1916) of patients with ordinary pulmonary tuberculosis, who had died from unassociated causes, had shown that the liver contained no tuberculous lesions. We have confirmed this observation in a further 10 cases. In primary tuberculosis hepatic follicles are seen more frequently than in the adult form, but less often than in miliary disease. Our own results and those of others show that epithelioid-cell follicles are found in about two-thirds of such cases (Table IX). Caseation is hardly ever seen in these lesions, so that liver biopsy gives no help in deciding between sarcoidosis and the primary or the less acute miliary forms of tuberculosis, and differentiation must be made on other grounds. The similar appearance of follicles found in the liver in sarcoidosis and in tuberculosis when there is no caseation is in harmony with the view that the two diseases are caused by the same organism. Histological evidence, however, cannot decide the issue, as it is known that epithelioid-cell follicles can be provoked by other agents. If the two diseases are eventually shown to have a common cause, then the similar frequency with which lesions are found in sarcoidosis and primary tuberculosis will be of especial importance. It would suggest that sarcoidosis represents an exaggerated and sometimes long-lasting reticulo-endothelial reaction following primary tuberculous infection.

We wish to thank all those colleagues who referred patients to our care; Professor H. A. Magnus and Dr. J. W. Clegg for the histological preparations and help in their interpretation; Professor C. H. Gray for the biochemical investigations; Dr. A. C. Cunliffe for the bacteriology; the Sisters of the medical wards who looked after the patients and the liver biopsy apparatus; and Mr. W. Smith and Mr. J. Harwood for the photomicrographs. Some of our expenses were defrayed by a grant from King's College Hospital Research Fund, and one of us (J. D.) was in receipt of a grant from the Brompton Hospital Research Fund. A large part of the work formed a thesis by one of us (G. M.) which has been accepted for the degree of M.D. (Cambridge).

APPENDIX

Technique of Liver Biopsy

Description of instrument. The instrument consists of a 2 mm.- or 1·8 mm.-bore needle mounted on a 20 ml. syringe, with a stilette fitted to the plunger (Fig. 1). The needle has a bevelled point, internally bored to give a sharp edge which produces a linear puncture of the liver capsule. The stilette point is made accurately to fit the bevel of the needle; the shaft has one flattened side, allowing suction from the syringe to be transmitted to the end of the needle. An adjustable depth-guard is fitted to the needle to prevent too deep a penetration.

The ratchet clip fitted to the syringe cap engages notches on the plunger rod, and thus holds the plunger in position after the specimen has been cut.

Preparation of the patient. All patients are admitted to hospital. No biopsy is attempted if normal liver dullness is absent, as from gross emphysema, pneumoperitoneum, or overlying bowel. A blood count is made, and bleeding, clotting, and prothrombin time and blood group determined; facilities for transfusion should be available. If an increased risk of bleeding is found the biopsy is either postponed or cancelled. All patients are given synthetic vitamin

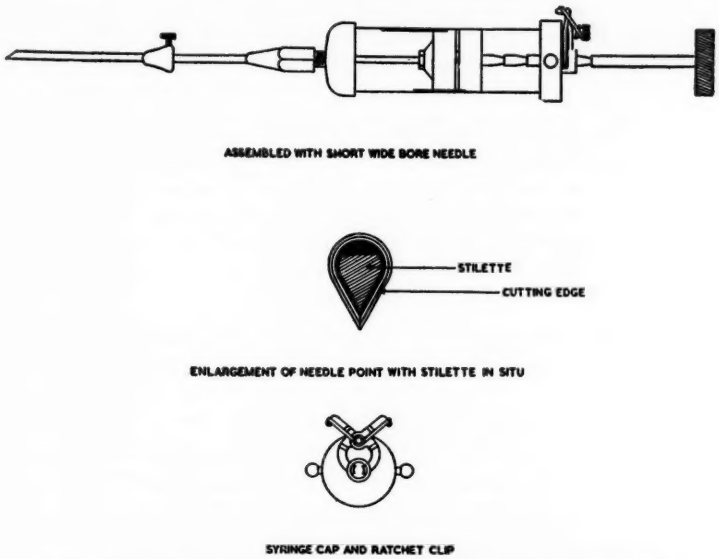
ASSEMBLED WITH SHORT WIDE BORE NEEDLE
STILETTE
CUTTING EDGE
ENLARGEMENT OF NEEDLE POINT WITH STILETTE IN SITU
SYRINGE CAP AND RATCHET CLIP

FIG. 1. The liver biopsy apparatus, approximately one-half natural size (W. H. Bailey & Son Ltd.).

K, 10 mg. daily, for two days prior to the biopsy. Half an hour before the procedure a sedative is given, usually an injection of papaveretum gr. 1/3 and scopolamine gr. 1/150. The biopsy is done in the ward.

Technique. The patient lies supine, with the right flank at the edge of the bed and the right hand beneath the head, and is well covered except for the lower ribs and upper abdomen on the right side. The skin is cleansed, and the site of puncture determined by percussion in full expiration and inspiration, to ensure that the selected point lies over the main mass of the liver; usually this point is in the eighth or ninth intercostal space in the anterior axillary line. Local analgesia is induced with 2 per cent. procaine solution, care being taken to infiltrate the diaphragm and liver capsule with the breath held in expiration. The skin is punctured with a small scalpel to facilitate entry of the needle. While full analgesia is developing the apparatus is assembled; a few drops of sterile liquid paraffin are used to lubricate the plunger. The depth-guard is adjusted to allow penetration of the liver to a depth of about 3 cm. The patient is rehearsed by instructing him to breathe in, then to breathe out, and then to stop breathing. If nervousness or other cause prevents the breath from being held in expiration for five seconds, the biopsy is not attempted, because of the danger of tearing the liver should respiratory movement occur while the needle

is inserted. To proceed, the biopsy needle is advanced through the intercostal muscles, and with the breath held in expiration it is then passed through the diaphragm into the liver. The left hand, holding the barrel and attached hollow needle, is next thrust forwards quickly for about 3 cm. down to the guard, and twisted round in order to detach the specimen; and the instrument is smartly withdrawn. Meanwhile the right hand, holding the handle of the syringe and attached stilette, is held still while the cutting needle is advanced. Thus a core of liver is cut out, and held within the needle by the suction transmitted from the syringe, the plunger being unable to move forward while the instrument is being withdrawn owing to the ratchet clip attached to its stem. The core of liver is gently ejected into a small glass tube in order to preserve its shape. A portion may be separated for bacteriological study; the remainder is placed immediately in 10 per cent. formol saline. A collodion dressing covers the skin puncture.

After-care. The patient is kept recumbent for six hours, and in bed for 24 hours. The pulse-rate is recorded every half-hour for two hours, hourly for four hours, and then four-hourly for 24 hours. Any rise in pulse-rate or complaint of severe pain is investigated, as either may indicate intra-abdominal haemorrhage. An injection of morphine may occasionally be needed.

Summary

Liver biopsy is a safe and reliable procedure for the diagnosis of sarcoidosis. Epithelioid-cell follicles were found in 59 (63 per cent.) of 93 patients with sarcoidosis, a frequency similar to that given in collected necropsy reports. The typical lesions and their variants are described. The frequency of hepatic follicles was irrespective of the degree of tuberculin sensitivity. They were as common in patients with pulmonary sarcoidosis (40 in 65 cases) as in those with bilateral hilar lymph-node enlargement only (18 in 25 cases), uveitis (14 in 18 cases), or splenic enlargement (nine in 13 cases). Follicles were found in 10 of the 11 patients in whom erythema nodosum heralded the onset of sarcoidosis. Only 10 of the 93 patients had a raised serum-globulin level, and there was no relationship between this abnormality and the presence of hepatic follicles. The natural history of hepatic sarcoidosis and the effects of treatment with streptomycin and cortisone were studied by means of serial biopsies in 31 patients.

Biopsies were taken from 32 patients with tuberculosis for comparison. Follicles similar to those found in sarcoidosis are common in miliary and primary tuberculosis, but are rare in the other forms. The significance of these observations in relation to the aetiology of sarcoidosis is discussed.

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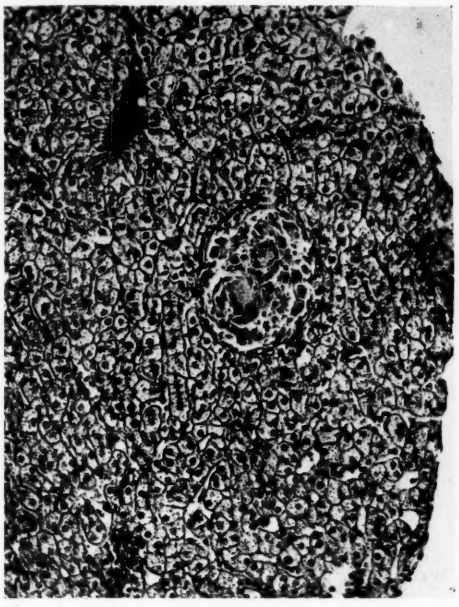


FIG. 2*a*. Liver biopsy from a patient with pulmonary sarcoidosis, showing a small epithelioid-cell follicle (haematoxylin and eosin. × 140)

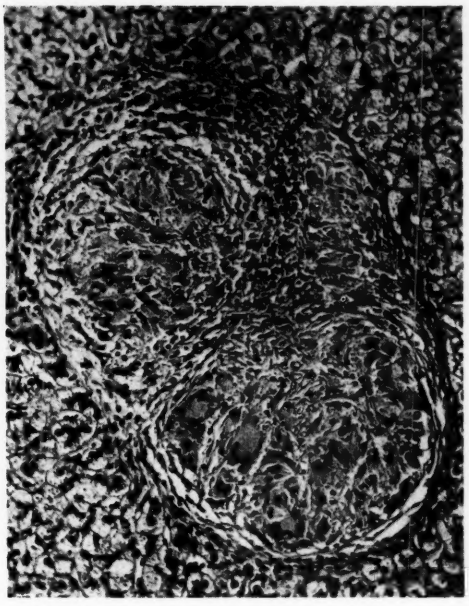


FIG. 2*b*. Liver biopsy from the same patient 16 months later, when the chest radiograph was almost normal. The follicle is much larger, but is of similar structure (haematoxylin and eosin. × 140)

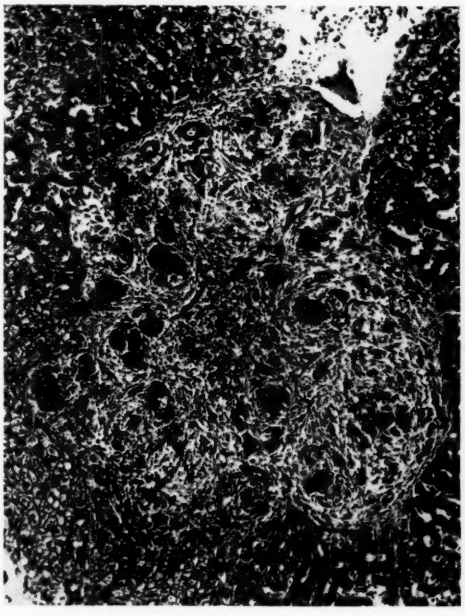


FIG. 3*a*. Hepatic follicle 700 μ in diameter from a patient with extensive pulmonary sarcoidosis. Abundant giant cells are seen, some with asteroid inclusion bodies (haematoxylin and eosin. × 70)

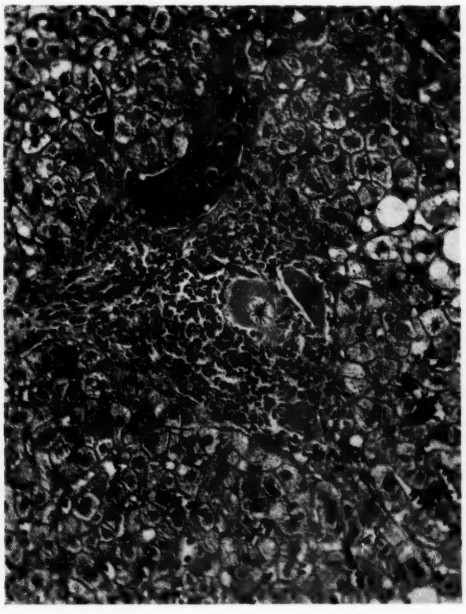


FIG. 3*b*. Biopsy from the same patient seven months later, after response to treatment with streptomycin and *p*-aminosalicylic acid. The follicle is much smaller, containing only lymphocytes and giant cells (haematoxylin and eosin. × 140)

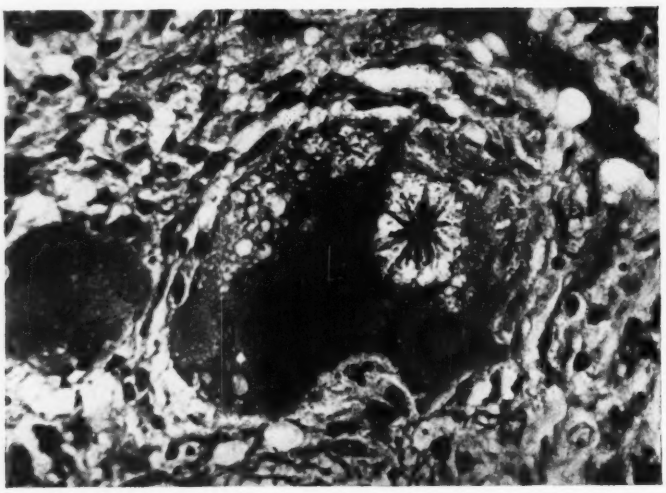
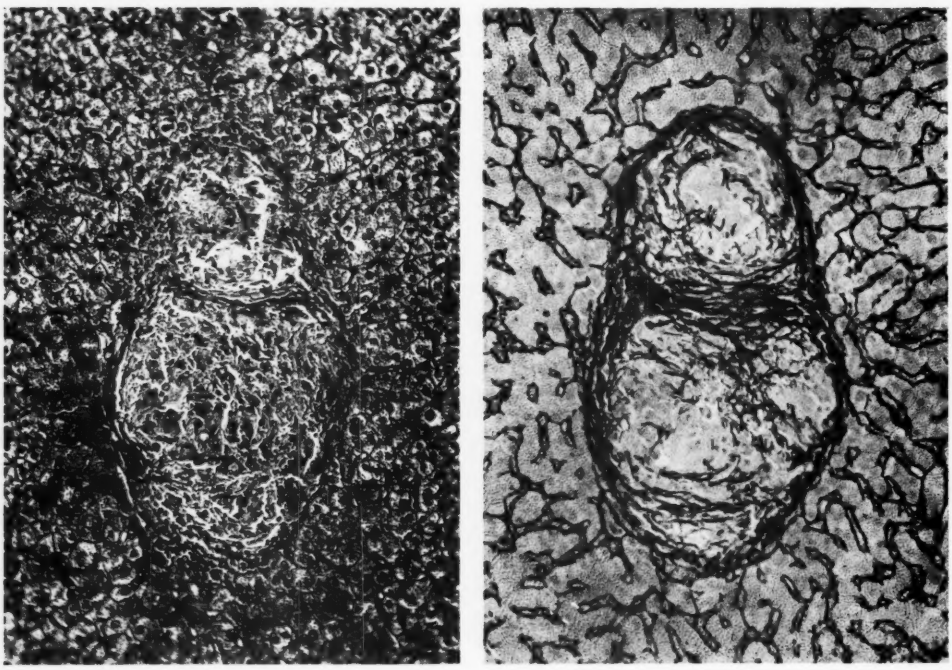
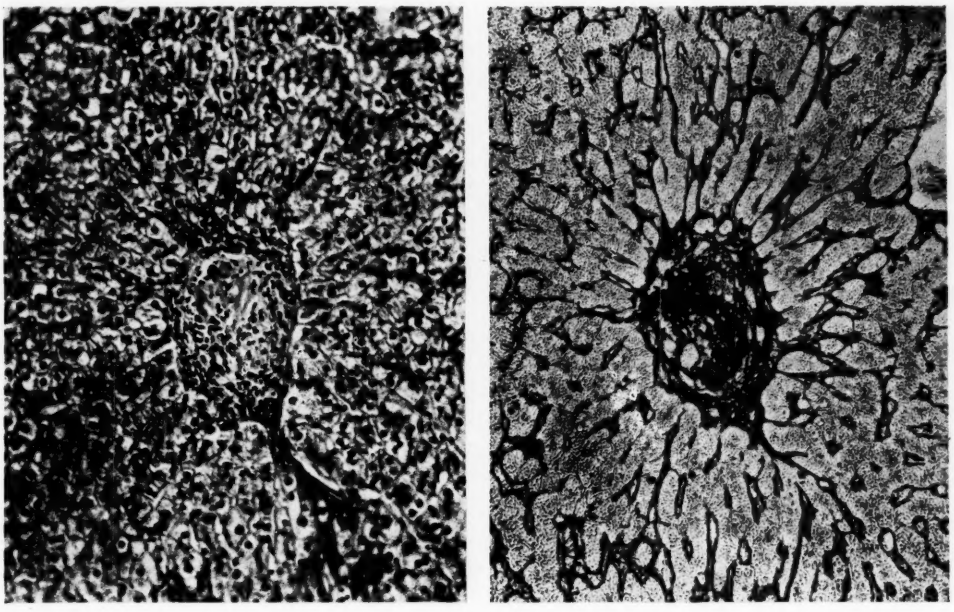


FIG. 4. Giant cell containing an asteroid inclusion body, from the same patient as Fig. 3*a* (haematoxylin and eosin. × 500)



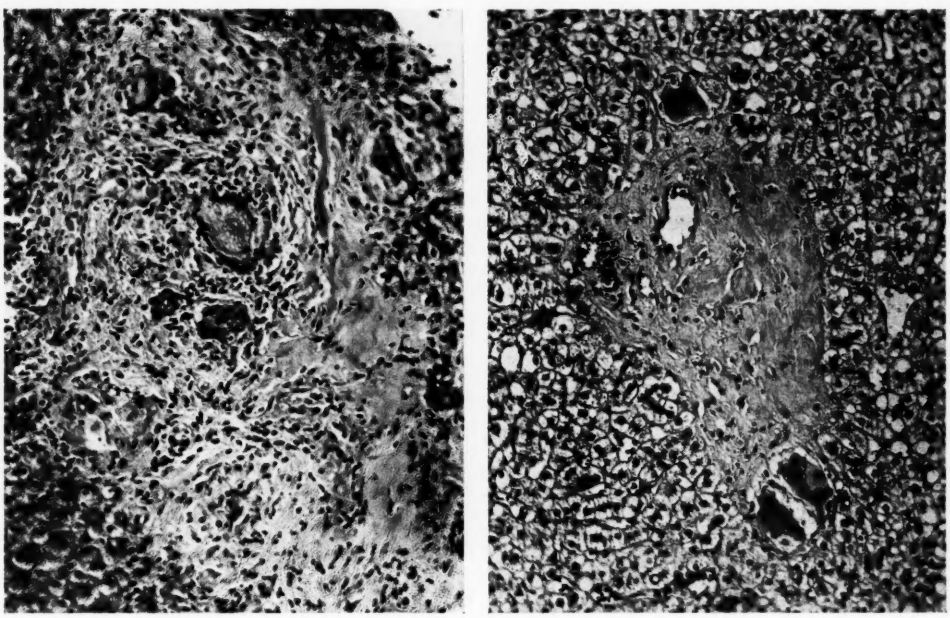
a *b*

FIG. 5. Hepatic follicle stained (*a*) with haematoxylin and eosin and (*b*) with Foot's reticulin stain, showing the incomplete reticulin network between the epithelioid cells and its condensation round the follicle (× 140). From a patient with pulmonary sarcoidosis of at least four years' duration



a *b*

FIG. 6. Biopsy from the same patient (Fig. 5): three months later, after clinical and radiographic improvement with cortisone and streptomycin. No follicles remained: the illustration shows some residual fibrosis and lymphocytes (× 140; *a*, haematoxylin and eosin; *b*, reticulin stain)



a *b*

FIG. 7*a*. Liver biopsy from a patient who had had pulmonary sarcoidosis for seven years. A band of hyaline fibrous tissue is seen round the follicles (haematoxylin and eosin. × 140)

FIG. 7*b*. Biopsy from the same patient two months later; there has been clinical and radiographic response to streptomycin and cortisone. No follicular structures are seen: the illustration shows portal tract fibrosis and three giant cells (haematoxylin and eosin. × 140)

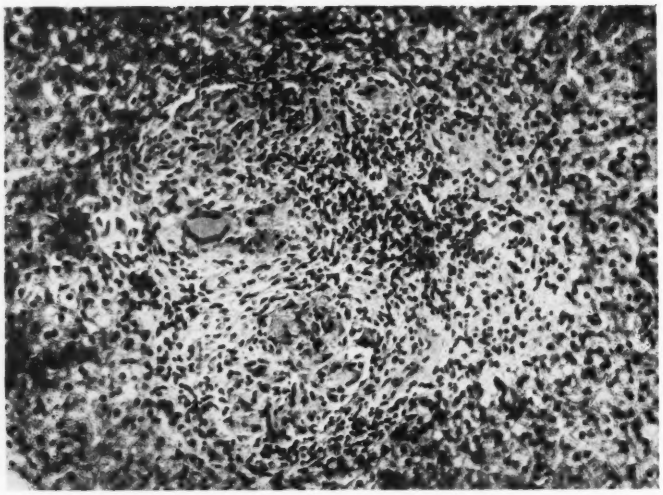


FIG. 8. Hepatic follicle from a patient with miliary tuberculosis. The structure resembles that seen in sarcoidosis; no necrosis is present (haematoxylin and eosin. × 140)

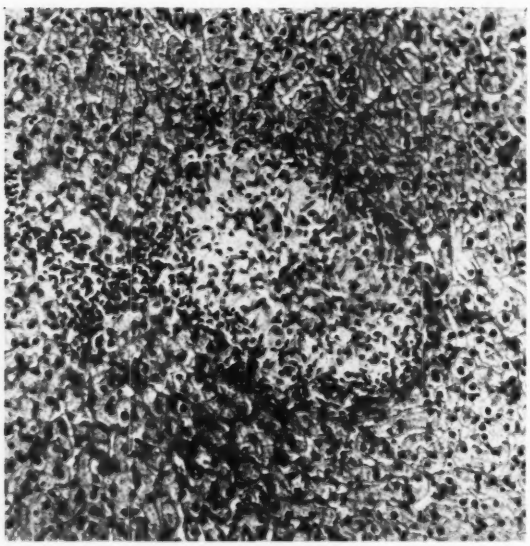


FIG. 9. Liver biopsy from a patient with primary tuberculosis and pleural effusion. An epithelioid-cell follicle without necrosis is shown, indistinguishable from sarcoidosis (haematoxylin and eosin. × 140)

616–002.511 : 616.155.194.7

TUBERCULOUS MILIARY NECROSIS WITH PANCYTOPENIA[1]

By W. E. MEDD and F. G. J. HAYHOE

(From St. Thomas's Hospital, London, and the Department of Medicine, University of Cambridge)

With Plates 42 and 43

Disseminated tuberculosis may give rise to such striking changes in the blood that the haematological manifestations dominate the clinical picture. A primary blood disorder may therefore be mistakenly diagnosed, and it is not until post-mortem examination has been carried out that the part played by tuberculosis is appreciated. These haematological complications of tuberculosis fall loosely into three groups: leukaemoid reactions, myelosclerosis with leuco-erythroblastic anaemia, and peripheral pancytopenia with normally cellular or hypoplastic marrow but no marrow fibrosis. The groups are not sharply differentiated; intermediate and transitional forms occur, just as they do between the primary diseases leukaemia, myelosclerosis, and idiopathic pancytopenia. In the present communication we describe four cases of peripheral pancytopenia associated with concealed disseminated tuberculosis, and draw attention to the clinical problems of diagnosis and treatment which arise in the management of such cases. In each case the histology of the tuberculous lesions was atypical, in that they consisted of miliary necrotic foci with but little cellular reaction.

Case 1. A 49-year-old Regular Army major was admitted to hospital on December 17, 1951 with a history of progressive weakness and lassitude for the previous 18 months. He had recently become short of breath on exertion. On examination he looked ill and anaemic, but there were no other significant findings. For the results of blood examination see the Table. He was given transfusions of four pints of blood in several days, but his general condition did not improve greatly. An enlarged, firm, painless gland became palpable in the right supraclavicular region, and crops of purpura appeared on the legs. On January 22, 1952 he was transferred to Addenbrooke's Hospital under the care of Sir Lionel Whitby. No additional clinical abnormalities were discovered, but on the day of transfer he developed for the first time a fever between 103° and 105° F., and this persisted throughout the remainder of his illness.

Investigations. Blood count: see the Table. The sternal marrow showed evidence of maturation arrest, with a high proportion of primitive white cells (neutrophile polymorphs, 15 per cent.; metamyelocytes: neutrophile, 5 per cent., eosinophile, 0·5 per cent.; myelocytes: neutrophile, 21·5 per cent., eosinophile, 0·5 per cent.; promyelocytes, 7·5 per cent.; myeloblasts, 12·5 per cent.; lymphocytes, 26 per cent.; monocytes, 0·5 per cent.; normoblasts: late, 7 per

[1] Received June 3, 1955.

Peripheral Blood Data

Transfusion indicated by T→

Patient, sex, and age (years)	*Date*	*Haemoglobin (gm./100 ml.)*	*White cells per c.mm.*						*Precursor cells*		*Platelets per c.mm.*	*Erythrocyte sedimentation rate (mm/1 hr.)**
			Total	*Neutrophils*	*Lymphocytes*	*Monocytes*	*Eosinophils*	*Basophils*	*Myeloid*	*Erythroid*		
1. W. E. B.	18.12.51	8	2,300	480	1,740	70	20	..	..	..	90,000	
	T→											
M. 49	25.1.52	9	2,750	1,200	1,200	270	30	30	20	..	90,000	31 (Win.)
	4.2.52	7·1	2,850	1,460	1,030	50	..	90	220	..	60,000	22 „
	15.2.52	3·4	1,900	870	1,000	20	..	..	..	..		
	T→											
	5.3.52	6	2,000	900	1,020	80	..	..	..	..		
	Splenectomy→8.3.52											
	14.3.52	8·6	6,600									
	19.3.52	8·4	9,700	5,800	3,600	190	100	..	..	..	76,000	..
	26.3.52	5·1	12,000	10,400	1,320	120	..	..	120	..		
	29.3.52	3·4	12,800	10,600	260	..	..	130	1,800	..		
2. S. K. M. 50	12.2.51	6	350	175	175	..	..	..	..	..		
3. A. M.	12.11.53	10·4	2,000	920	1,000	40	40	..	..	..	80,000	
	4.12.53	8·9	1,300	1,040	180	60	20	..	..	..	100,000	70 (West.)
	28.12.53	6·3	4,400	3,040	1,100	130	40	90	..	..	180,000	110 „
M. 49	25.1.54	10	2,750	1,460	1,100	110	80	..	..	..		
	9.3.54	14	2,750	1,680	910	80	50	30	..	..		55 „
	7.4.54	12	3,200	1,640	1,560	..	..	..	..	..		37 „
	10.5.54	12·5	3,550	1,950	1,420	70	110	..	..	..		34 „
	3.6.54	13·4	2,200	1,100	1,000	100	..	..	..	..		19 „
	30.8.54	13	3,100	1,860	1,110	70	60	..	..	..		28 „
	23.11.54	12·7	2,200	1,430	660	20	90	..	..	..		31 „
4. H. W.	12.9.53	3·6	1,400	170	1,230	..	..	..	..	..	146,000	
	T→											
	T→											
F. 56	15.3.54	7·1	700	70	620	..	10	..	..	..	..	
	T→											
	21.4.54	8·7	1,150	160	990	..	..	..	..	..	150,000	34 (Win.)
	10.5.54	9·4	2,000	800	1,100	40	..	..	20	40	150,000	12 „
	21.6.54	6·3	1,000	200	780	..	..	..	20	..	80,000	36 „
	1.7.54	5·4	800	220	580	..	..	..	..	..	60,000	35 „

*Win. = Wintrobe, corrected. West. = Westergren.

cent., intermediate, 2·5 per cent., early, 1·5 per cent. The myelo-erythrogenetic ratio was 5·5:1). Blood culture was sterile, and stool culture grew no pathogens. A chest X-ray showed two small opacities in the second right intercostal space, which were considered to represent healed tuberculous foci. No acid-alcohol-fast bacilli were seen in three specimens of sputum. Agglutination reaction to *S. typhi* was positive to 1 in 5,000, and to *S. paratyphi* B H positive to 1 in 1,000 (he had received T.A.B. injections previously), but *S. typhi* O and *Brucella abortus* agglutinations were negative.

No firm diagnosis was made to account for the pancytopenia, but the possibility of underlying miliary tuberculosis was considered. He was transferred back to the other hospital on February 7. His spleen was then found to be just palpable, and his general condition steadily worsened. Repeated transfusions failed to raise his haemoglobin to over 7 gm. per 100 ml. On March 8 laparotomy was performed and the spleen, enlarged to three times normal size, removed. Histological examination of a section from the spleen was reported as follows: 'A section of spleen shows a granulomatous lesion (1 mm. in diameter approximately) lying a short distance below the capsule. This has a necrotic centre containing granular material, nuclear fragments, and polymorphonuclear leucocytes and lymphocytes. At one pole there are many epithelioid cells. There is much haemosiderin elsewhere in the splenic tissue. Five fine beaded acid-fast bacilli have been identified in Ziehl-Neelsen stained sections. The appearances in the necrotic lesion strongly suggest that the lesion is tuberculous.' Culture of material from the spleen grew tubercle bacilli later. After splenectomy the leucocyte count increased remarkably (see Table), but the patient's general condition deteriorated, and in spite of further blood transfusions he weakened and died on March 30.

At post-mortem examination the left pleural cavity contained about two pints of straw-coloured fluid. The lower lobe of the left lung was congested. On section a fair number of tiny white tubercles were visible. The upper lobe and the right lung showed an occasional tubercle. No larger focus was seen. The liver was pale. On section it was found to be heavily studded with pin-head sized tubercles. The bone-marrow appeared normal. Several right cervical and mediastinal lymph-glands were found enlarged and caseous. A mass of four or five caseous glands, each about two inches in diameter, was found in the portal fissure. Scanty tubercles, just visible to the naked eye, could be seen in some of the cerebral fissures. The base of the brain appeared clear. The histological findings were as follows. Cervical gland: areas of caseation are surrounded by chronic inflammatory cells, among which epithelioid cells predominate. There are a few giant cells, and the whole picture is one of tuberculosis. Abdominal glands: there are caseating tuberculous glands, in which acid-fast bacilli can be seen. Liver: there is a large number of foci of miliary necrosis. The larger ones (Plate 42, Fig. 1) are mostly cuffed by a mixed inflammatory reaction, the cells being chiefly histiocytes and polymorphs; some are diffusely infiltrated with these cells. Lung: there is a focus of necrotizing granulomatous pneumonia, with an appearance similar to that seen in the liver. Cerebral cortex: the brain surface shows a thin exudate, in which a well-marked, compact group of lymphocytes and epithelioid cells can be seen.

Case 2. A Greek Cypriot farmer, aged 50 years, was admitted to a hospital in Nicosia, Cyprus, on February 12, 1951 under the care of Dr. J. E. O'N. Gillespie, with a history of two months' progressive weakness. His condition was so bad that no further details could be obtained. On examination he was pale and short of breath. His temperature was 103° F., and his pulse-rate 125. There

*Win. = Wintrobe, corrected. West. = Westergren.

were fine crepitations at both lung bases, and oedema of the legs. The urine contained a trace of albumin.

Investigations. A blood count showed haemoglobin 42 per cent. (6 gm. per 100 ml.), red cells 2,000,000 per c.mm., and white cells 350 per c.mm. (polymorphs 50 per cent. lymphocytes 50 per cent.). The blood film showed normocytosis and normochromia. A slide of the sternal marrow was sent later to Sir Lionel Whitby, and showed a moderately cellular marrow with maturation arrest, myelocytes and promyelocytes predominating (neutrophile polymorphs, 0·5 per cent.; metamyelocytes: neutrophile, 4·5 per cent., eosinophile, 1 per cent.; myelocytes: neutrophile, 77·5 per cent., eosinophile, 0·5 per cent.; promyelocytes, 7·0 per cent.; myeloblasts, 0·5 per cent.; lymphocytes, 2 per cent.; plasma cells, 2 per cent.; normoblasts: late, 2·5 per cent., intermediate, 1·5 per cent.; reticulum cells, 0·5 per cent. The myelo-erythrogenetic ratio was 20:1. Mitotic figures were seen in 10 per 1,000 nucleated cells). A chest X-ray showed no lung lesion.

A diagnosis of aplastic anaemia was made, but in spite of blood transfusions and penicillin his temperature and pulse-rate remained high, and his condition steadily deteriorated, until his death five days after admission. Post-mortem examination revealed large masses of glands in the superior mediastinum and in the retroperitoneal space. The liver and spleen were of normal size, but showed numerous white miliary nodules about 1 mm. in diameter; some of them appeared to be calcified. Histological preparations were also sent to Cambridge, and were examined by Dr. A. M. Barrett, who reported as follows: 'Retroperitoneal lymph-node: caseous tuberculosis. Vast numbers of acid-alcohol-fast bacilli are present. The cellular reaction is of slight degree, and is unlike that generally seen in tuberculosis. Liver: caseous miliary tuberculosis. As in the lymph-node, there is only slight cellular reaction; the tubercles are little more than focal necrosis' (Plate 42, Fig. 2). 'They contain abundant acid-alcohol-fast bacilli.'

Case 3. A man aged 49 years, a bus driver, was seen at St. Thomas's Hospital on October 28, 1953, complaining of feeling weak and unwell for three weeks. His friends had told him he looked pale and ill. He had lost his appetite, and on one or two occasions had vomited. He had noticed excessive sweating, and had lost about one and a half stone in weight. On examination he was anaemic, but did not look seriously ill. The spleen was enlarged to three fingers' breadth below the left costal margin. A tentative diagnosis of splenic anaemia was made. For the blood count see the Table. He was admitted for investigation under the care of Dr. Evan Jones on November 11, and during the fortnight of waiting for admission his general health had deteriorated considerably. He had also had a rash on the trunk for the five days previous to admission. On examination he looked pale and toxic. His temperature was 102° F., his pulse-rate 90, and his respirations 18 per minute. He had a vivid erythematous rash all over the trunk, with superimposed red macules; these faded on pressure, except in a few instances, especially on the buttocks, where they appeared to contain a little extravasated blood. There were no enlarged lymphatic glands. The edge of the liver was just palpable, but the liver did not seem to be enlarged. The spleen was palpable to four fingers' breadth below the costal margin; it was firm, and not tender. His urine contained albumin, but no abnormality was found in any other system.

Investigations. For the main blood counts see the Table; reticulocytes were less than 1 per cent. The sternal marrow, diluted with blood, showed mild normoblastic hyperplasia (segmented polymorphs: neutrophile, 9·5 per cent., eosinophile, 1 per cent.; neutrophile band polymorphs, 15 per cent.; neutro-

phile metamyelocytes, 7·25 per cent.; myelocytes: neutrophile, 6 per cent., eosinophile, 0·25 per cent.; promyelocytes, 0·25 per cent.; lymphocytes, 17 per cent.; monocytes, 0·5 per cent.; plasma cells, 0·5 per cent.; leucoblasts, 0·25 per cent.; smear cells, 20·5 per cent.; normoblasts: basophile, 1·75 per cent., polychromatic, 18·25 per cent., orthochromatic, 1·75 per cent. The leuco-erythrogenetic ratio was 1·35:1). Repeated blood cultures were sterile, and stool cultures showed no pathogens. Chest X-rays showed no abnormality throughout his illness. The blood Wassermann and Kahn reactions were negative, and lumbar puncture showed a normal cerebrospinal fluid. Agglutination reactions to *S. typhi* H and *S. paratyphi* B H were positive to 1 in 250, and to *S. paratyphi* C H and *Brucella abortus* negative. He had received T.A.B. injections during the war, and a fortnight later these agglutination tests were repeated with the same results. *S. typhi* O, and *S. paratyphi* A O, B O, and C O agglutinations were negative. The direct Race-Coombs test was negative. Urine urobilinogen excretion on two separate occasions was 14·2 mg. and 0·1 mg. in 24 hours. Serum-bilirubin on two separate occasions was 1 mg. and 0·5 mg. per 100 ml. The erythrocyte sedimentation rate was 110 mm. in one hour (Westergren).

The rash faded in a few days, but he continued to have a fever (101° to 102° F.), and his general condition became steadily worse. He was given penicillin, one mega unit twice daily, for three days, and terramycin, 500 mg. six-hourly, for six days, without any effect. In view of our experience in Case 1 miliary tuberculosis was considered possible, and an aspiration liver biopsy, performed nine days after the patient's admission, showed acute miliary tubercles (Plate 42, Figs. 3 and 4). Treatment was started with streptomycin 1 gm. daily, *p*-aminosalicylic acid 4 gm. six-hourly, and isoniazid 50 mg. thrice daily. During the next few days his condition became desperate, but after a week's treatment his temperature began to fall, and he felt better. Ten days after its commencement he developed an allergic reaction to *p*-aminosalicylate, and this drug was discontinued. Later he became allergic to the streptomycin, but was successfully desensitized. His improvement continued slowly, and his first normal evening temperature was recorded six weeks after starting treatment with streptomycin and isoniazid. A second liver biopsy was performed four months after the start of treatment, and showed the following changes. There were occasional foci of fibrous replacement of liver-cells, associated with chronic inflammatory-cell infiltration (Plate 43, Fig. 5). It seemed that these foci could well represent healed or healing lesions of the necrotic type seen in the original biopsy. In addition one large and one smaller (Plate 43, Fig. 6) granuloma, of the sort seen in sarcoid liver biopsies, were seen, consisting of swollen histiocytes cuffed by a small zone of lymphocytes. There was slight chronic inflammatory-cell infiltration of the portal tracts. The patient's weight increased from 9 st. 5 lb. at the start of his illness to 12 st. 12 lb. during the next year. The dosage of streptomycin was reduced to 1 gm. on alternate days after five months' treatment, and to 1 gm. twice weekly after seven months. Isoniazid was continued at the same dose throughout. When examined 15 months after the start of treatment he felt absolutely well, apart from pain due to osteo-arthritis of the hips, which had developed while he was in hospital. The only abnormal physical finding was that his spleen was still palpable two fingers' breadth below the costal margin, though it was smaller than at the start of his illness. In view of this, and because leucopenia and slight anaemia persisted (see Table) and the erythrocyte-sedimentation rate was still 17 mm. in one hour, chemotherapy was continued, although he was allowed to resume light work.

Case 4. A 56-year-old female patient was first admitted to hospital in September 1953. She had been healthy until about nine months previously, when several transient purple, painless, subcutaneous nodules had appeared on the lower legs, and she subsequently had an upper respiratory infection. Although both the nodules and the respiratory infection cleared up, there was from this time a gradual onset of weakness and loss of energy, and by August 1953 she was dyspnoeic on exertion and pale. She had no cough or pain in the chest. There was no past history or family history of tuberculosis, and there had been no loss of weight. Examination on admission showed severe anaemia, but no glandular or splenic enlargement. She was febrile, and had several skin lesions suggestive of erythema nodosum, but there were no other positive physical findings. The peripheral blood (see the Table) showed gross anaemia and neutropenia with moderate thrombocytopenia. An aspirate of sternal marrow was very poor in cells, with an increased proportion of plasma cells, and a trephine biopsy showed hypoplasia, with occasional islets of normal haemopoietic tissue, but no fibrosis or neoplastic infiltration. Several blood cultures were sterile; hepatic function tests were normal; sections of a biopsy specimen from one of the erythematous nodes showed non-specific vasculitis only; X-rays of the chest and skeleton were normal.

At this stage a diagnosis of aplastic anaemia was made, and she was treated with several blood transfusions, oral iron, and intramuscular penicillin. When she had been about two months in hospital a considerable improvement ensued, not clearly related to therapy, and she was observed as an out-patient until March 1954, when a sharp relapse took place, with bruising on the shoulders, back, and arms, purpuric spots in the mouth, and increase in pallor. She was readmitted to hospital and given a transfusion; some improvement followed, and in April a further sample of marrow was aspirated. This specimen was, surprisingly, very cellular, and seemed typical of acute leukaemia, with 65 per cent. primitive cells, probably myeloblasts, and 15 per cent. cells of the normoblast series. In view of this finding the disease was now considered to be aleukaemic myeloblastic leukaemia with previous aplastic phases, and treatment with cortisone was started. The patient's general condition was remarkably improved after a week of 200 mg. cortisone daily; the haemoglobin level had risen by 1 gm. per 100 ml., there was a reticulocytosis of 9 per cent., and the leucocyte count returned towards normal. She was discharged again at this stage, taking a maintenance dose of 75 mg. cortisone daily, and the improvement continued for a further month. After this interval a relapse occurred again, and she was readmitted to hospital at the end of June 1954 with gross dyspnoea and pallor, and with signs of extensive pleural effusion in the right side. There was high fever, which responded to terramycin, but the clinical state continued to deteriorate rapidly, and death occurred early in July. Cortisone had been discontinued upon admission in view of the probable chest infection.

Post-mortem examination showed, macroscopically, a large right pleural effusion and complete collapse of the right lung, but no other significant abnormal findings. The red marrow showed some extension into the femoral shafts, but was pale in colour and predominantly fatty. No glandular or splenic enlargement was found, and the liver appeared normal. Microscopic study of sections, however, revealed areas of caseation, with infiltration with epithelioid cells and lymphocytes, in both visceral and parietal pleura on the right side, and similar though less conspicuous tuberculous lesions were found in the cervical and tracheobronchial lymph-nodes (Plate 43, Figs. 7 and 8). The lesions contained demonstrable acid-alcohol-fast bacilli. The marrow, which was fatty

and hypoplastic, did not show leukaemic changes in the sections made, nor did it contain tubercles or focal areas of necrosis. Tuberculous lesions were not found in the liver, lungs, spleen, kidneys, suprarenals, or heart.

Discussion

Historical. The features common to these four patients are pancytopenia and a type of miliary tuberculosis which is unusual in that, histologically, the lesions are those of miliary necrosis with little cellular reaction but, in the three patients who died, containing abundant tubercle bacilli. The clinical picture in the later stages of high fever and leucopenia often suggests typhoid fever, and Landouzy (1891) first drew attention to atypical cases of miliary tuberculosis which had this resemblance. He also noted that the microscopic lesions were *prégranulique*, rarely forming typical tubercles. Gougerot (1912) again contrasted the appearances of necrosis in this type of miliary tuberculosis with the granulomatous follicle of the ordinary type, and Reiche (1914) was apparently the first to observe tubercle bacilli in the lesions in this condition. Scholz (1918) described a case, and termed the condition 'sepsis tuberculosa acutissima with miliary tuberculosis'. Similar cases have since been reported under various titles, for example, tuberculous splenomegaly (Engelbreth-Holm, 1938), tuberculous septicaemia and Landouzy's typho-bacillus (von Wyss, 1940), fulminant tuberculous septicaemia (Blair and Pagel, 1947; Pagel and Woolf, 1949), acute tuberculous septicaemia with leucopenia (Ball, Joules, and Pagel, 1951), atypical abdominal tuberculosis with haematological manifestations (Friend and Thackray, 1952), and tuberculous portal pyaemia (Leggat, Jones, and Taylor, 1953). All these patients died, and in only the last case mentioned, in which there was associated pulmonary tuberculosis, was the diagnosis made in life. Fountain (1954) described four similar fatal cases, in one of which the diagnosis was made in life by gland biopsy, but gave no details concerning the histology of the miliary tubercles. Paulley (1954) treated a girl who had high fever and pancytopenia, with no histological proof of the diagnosis, by means of streptomycin and isoniazid, and apparent cure resulted, although the case had only been followed up for two months. Since effective treatment has become available, the clinical picture and means of diagnosis should be better known to the general physicians and haematologists into whose hands these cases usually fall.

Clinical features. Our four patients ranged in age from 49 to 56 years (average 51) and consisted of three men and one woman. A preponderance of middle-aged male patients was also noted by Ball, Joules, and Pagel (1951); in their 11 cases (three of their own and eight from published reports) the patients' ages varied from 22 to 56 years, with an average of 44, and there were eight men and three women. Three of our patients initially presented an anaemia of obscure origin, and then after an interval of a few weeks became seriously ill with high fever and toxaemia. The remaining patient came to hospital only in the terminal stages of the illness, and it is not known whether there was a preliminary stage of anaemia only. If the patient seeks medical advice early,

the case is likely to be regarded as haematological, and the diagnosis of miliary tuberculosis may not be considered, the peripheral blood findings being suggestive of aplastic anaemia, 'Banti's syndrome', or possibly an aleukaemic leukaemia. In the later stages the patient is likely to come under observation with unexplained fever, and the association of splenomegaly and leucopenia may suggest typhoid fever.

Diagnosis. The clinical combination of high fever, sweating, and loss of weight with pancytopenia should readily suggest the condition. There will sometimes be a palpable spleen, as in two of our cases, and occasionally a rash. A rash was only seen in one of our patients, but was recorded in three of the 11 cases collected by Ball, Joules, and Pagel (1951). Ordinary methods of confirming the diagnosis of miliary tuberculosis may not be applicable. Choroidal tubercles were not seen in any of our four patients, nor was there any miliary shadowing in their chest X-rays. Accordingly aspiration liver biopsy, which was first used to diagnose miliary tuberculosis by Craddock and Meredith (1949), and by which our Case 3 was diagnosed, seems likely to be the most useful method. The histology of the miliary lesions is atypical, in that they appear as focal areas of necrosis with little cellular reaction, so that giant cells are often absent. The second liver biopsy in Case 3 is of particular interest, as it was done four months after the commencement of treatment, when the patient showed very marked clinical improvement; the section showed much greater cellular reaction than on the first occasion. Acid-fast bacilli were not seen in the original liver biopsy in Case 3, although they were seen in considerable numbers in the post-mortem liver sections in Cases 1, 2, and 4, and in all the three cases reported by Ball, Joules, and Pagel. The reason for their absence is not clear; it is possible that the biopsy specimen was comparatively small, but acid-fast bacilli were present in the specimen obtained by aspiration biopsy by Craddock and Meredith (1949). Löwenstein culture of biopsy material from the liver of our patient was not attempted, but will be tried in any future case. Aspiration liver biopsy will not establish the diagnosis in all cases, since in some (for example Case 4) the liver shows no lesions even when examined microscopically *post mortem*.

Other possible diagnostic methods, not used in our cases, may be applicable. Biopsy of the enlarged supraclavicular gland would have provided suggestive evidence in Case 1, as it was found to be a caseating tuberculous gland at post-mortem examination. Histological section or Löwenstein culture of a bone-marrow biopsy specimen has never been used in this condition, but might provide the diagnosis, since involvement of the bone-marrow was seen *post mortem* in all the three cases reported by Ball, Joules, and Pagel (1951), in the two cases of von Wyss (1940), and in one of those reported by Siegmund (1939). Trephine biopsy of the bone-marrow was not attempted in any of our patients; the bone-marrow was examined *post mortem* in only one of the three patients who died (Case 4), and no tuberculous foci were seen. In the ordinary type of miliary tuberculosis, however, miliary tubercles were found in an aspiration specimen of bone-marrow by Stahel (1939) in one case, and by Schleicher (1946)

in eight cases, and in five of the instances reported by Schleicher tubercle bacilli were seen in the lesions. Horowitz and Gorelick (1951) studied bone-marrow obtained by aspiration from the iliac crest in 20 patients, most of whom had advanced pulmonary tuberculosis; 14 cases showed acid-fast bacilli on direct smear, and five of these specimens also grew tubercle bacilli on culture. Emery and Gibbs (1954) found histological tubercles *post mortem* in 13 of 44 children who died of miliary tuberculosis, in a volume of bone-marrow which they estimated could have been obtained by aspiration during life. Aspiration biopsy of the spleen, and histology and Löwenstein culture of the material obtained, might give diagnostic information, since the spleen was found macroscopically and microscopically to be involved in two of the three cases of the present series in which it was available for examination; one of these specimens was examined after splenectomy, and a culture taken from the spleen grew tubercle bacilli; the other was examined *post mortem*, and showed numerous acid-fast bacilli in the lesions, but no culture was made. In the remaining case which came to post-mortem examination the spleen was macroscopically normal, but showed one tuberculous nodule in the two histological sections examined. The technique of spleen biopsy, however, is less well established, and aspiration biopsy of the liver seems preferable unless the spleen is considerably enlarged. The last tissue that might be suitable for biopsy is the skin, when lesions are present in it.

Treatment. Without treatment this type of tuberculosis is always rapidly fatal, and we have been unable to find any previous histologically proved case in which treatment has been successful. The patient of Leggat, Jones, and Taylor (1953) showed initial improvement and subsequent deterioration; treatment, however, was only continued for three months, and the patient also had pulmonary tuberculosis with a positive sputum. One of our patients (Case 3) responded steadily but slowly, and his first normal evening temperature was not recorded until six weeks after the start of chemotherapy. He has so far been treated for 16 months and, although he has gained three and a half stone in weight and is symptomless, his erythrocyte-sedimentation rate is still raised to 17 mm. in one hour (Westergren), and the leucopenia persists (see the Table), although the haemoglobin level is now normal. It is proposed to continue chemotherapy until the erythrocyte sedimentation rate becomes consistently normal. As regards the details of treatment, streptomycin, 1 gm. daily by intramuscular injection, with isoniazid 50 mg. thrice daily, was used in this case. After five months' treatment the streptomycin dosage was reduced to alternate days, and after seven months to twice weekly, isoniazid being continued in the above dose throughout. After 15 months' treatment the patient was allowed to resume light work. The question arises whether, in cases of aplastic anaemia of unknown aetiology, treatment with streptomycin and isoniazid should be used on the grounds that the patient might be suffering from a concealed disseminated tuberculosis. Clearly every effort, including aspiration liver biopsy, should be made to make a firm diagnosis, but in the present state of knowledge there will probably be patients, especially those with considerable fever, who must be

treated empirically. This was done, without liver biopsy, by Paulley (1954) with good effect. Further investigation may determine to what extent the available methods of diagnosis, such as liver, marrow, and spleen biopsy, can be relied upon; the number of patients treated without diagnostic proof should then diminish. It is important to realize that improvement may not start for one or more weeks, and that if there is improvement treatment may have to be continued for a year or more to prevent relapse.

The histological features and their pathogenesis. The histology of the miliary tuberculous follicles was unusual in all these cases. In all of them the majority of the follicles consisted of small zones of necrosis (this term is used as synonymous with caseation) with little or no surrounding infiltration with histiocytes, lymphocytes, or giant cells. Examples of this type of lesion are three of the four follicles in the first biopsy specimen from the liver in Case 3 (Plate 42, Fig. 4), the specimens from the liver (Plate 42, Fig. 2) and spleen in Case 2, from the liver (Plate 42, Fig. 1), lung, and lymph-gland in Case 1, and some parts of the lymph-gland section in Case 4 (Plate 43, Fig. 7). Acid-fast bacilli were seen in the lesions in appropriately stained sections of the liver and spleen in Case 2, of the spleen in Case 1, and of the lymph-glands in Case 4; they were not seen in the liver biopsy specimen in Case 3. In the spleen in Case 1 there was a greater cellular reaction with histiocytes, but these lesions also contained acid-fast bacilli. One of the follicles in the liver in Case 3 (Plate 42, Fig. 3), and a minority of the lesions in the lymph-glands in Case 4 (Plate 43, Fig. 8), showed typical tuberculous granulation tissue, with histiocytes, lymphocytes, and giant cells. It seems possible that the slightly increased cellular reaction in some of the lesions in Cases 1 and 4 may be attributed to the fact that the disease was probably of longer standing in these patients than in Cases 2 and 3, in which almost all the lesions were purely necrotic. The second liver biopsy in Case 3, taken four months after treatment had started, is of interest in that it showed occasional foci of fibrous replacement of liver-cells associated with chronic inflammatory cell infiltration (Plate 43, Fig. 5). It seemed likely that these foci were healed or healing lesions of the necrotic type seen in the biopsy before treatment. In addition two foci were seen which resembled sarcoid granulomata (Plate 43, Fig. 6).

Yersin (1888) produced miliary necrotic lesions in rabbits by the intravenous injection of tubercle bacilli. Gougerot (1912), in similar experiments, found that large doses of virulent bacilli produced purely necrotic lesions, whereas smaller doses of less virulent bacilli produced tubercles with the normal reaction. Scholz (1918) compared the lesions in his patient with the areas of miliary necrosis, full of tubercle bacilli, resulting from the intravenous injection of tubercle bacilli into monkeys, and this work has been extended by Rich (1944). These findings, together with the fact that large numbers of bacilli have been seen in the lesions in most reported cases, suggest that this type of necrotic lesion is a result of the invasion of over-sensitive or susceptible tissues by unusually virulent organisms or an unusually large number of bacilli. In view of the almost constant post-mortem finding of tuberculous glands, it is probable that

the bacilli gain a sudden entry into the blood-stream in large numbers by rupture of a gland into a vein.

The mechanism of the blood changes. The four cases presented above are all examples of peripheral pancytopenia. The severity of involvement of leucocytes, red corpuscles, and platelets varies from case to case (see Table), and the bone-marrow samples range in cellularity from normal to frankly hypoplastic, with differing degrees of preponderance of primitive cells of the myeloid series, amounting in Case 4 to a picture apparently typical of acute leukaemia, and in Case 1 to 20 per cent. of promyelocytes and myeloblasts, while in Case 2 the marrow showed an increase chiefly of myelocytes and promyelocytes, and in Case 3 the count was within normal limits. Splenomegaly has not been a constant feature in our cases, and this fact, with the tendency to marrow hypoplasia and the absence of evidence of haemolysis, suggests that hypersplenism was not of major pathogenetic importance. Direct invasion of the marrow, with focal areas of necrosis and miliary tubercles, is also not a constant feature in the post-mortem findings. Such invasion was not demonstrated in any of our cases, and in previously recorded cases in which it was present it was clearly not on so massive a scale as to account, by replacement and destruction, for the great loss of haemopoietic activity.

It seems possible that the leukaemoid, myelosclerotic, and pancytopenic blood complications of acute tuberculosis may share not only a common cause but an essentially similar pathogenetic mechanism. Leukaemoid reactions may mimic myeloid (Custer and Crocker, 1932; Leibowitz, 1938; Friend and Thackray, 1952), lymphocytic (Landon, 1925; Gardner and Mettier, 1949), or monocytic (Gibson, 1946) varieties of leukaemia, and are commonly like the acute or subacute forms of that disease. Aleukaemic blood findings in a lymphatic leukaemoid reaction to tuberculosis have been described, however, by Staffurth and Spencer (1950), and one of our patients (Case 4) at one stage of her illness showed similar features in the blood and marrow, resembling those seen in acute aleukaemic myeloblastic leukaemia. Tuberculous myelofibrosis closely parallels the idiopathic form of this disease in clinical and haematological features. Crail, Alt, and Nadler (1948) described four such cases, and collected from published reports seven others, in which acute caseating tuberculosis was considered to be responsible for the bone-marrow fibrosis. In a footnote to their paper, however, they mentioned a patient with a leuco-erythroblastic anaemia, who was found at autopsy to have miliary tuberculosis and a hypoplastic marrow without fibrosis. Leucopenia and pancytopenia in acute tuberculous septicaemia was observed by Ball, Joules, and Pagel (1951) in three patients, and they collected eight similar cases from published reports. Case 4 in the present communication illustrates very well how closely related such pancytopenic pictures may be to leukaemoid reactions. Further, a peripheral blood picture characteristic of polycythaemia rubra vera was seen in a case of miliary tuberculosis described by Guild and Robson (1950). We suggest that these superficially different haematological responses to acute tuberculosis are fundamentally similar. The corresponding primary blood disorders are themselves

probably closely related, leukaemia and myelosclerosis being regarded by many authorities as variants of a general 'myeloproliferative syndrome' (Heller, Lewisohn, and Palin, 1947; Dameshek, 1951; Hutt, Pinniger, and Wetherley-Mein, 1953), while aplastic pancytopenic phases may occur terminally in, or during the course of, either of these diseases. A hypothetical marrow-stimulating principle has been invoked as a possible active agent in the pathogenesis of the primary 'myeloproliferative' disorders. Increased marrow activity after the administration of corticotrophin (Dameshek, 1950) and the myeloid metaplasia produced by crude pituitary extracts and testosterone (Selye and Stone, 1950) lend some support to the idea that this hypothetical factor may be hormonal.

The comparable haematological disorders due to tuberculosis may share a similar common pathogenetic mechanism, the active principles here being the products of the tubercle bacillus acting on over-sensitive, 'allergic' haemopoietic tissues. In almost all reported cases of such tuberculous blood dyscrasias the disseminated tuberculosis has been atypical histologically, being characterized by multiple necrotic foci in various organs with little surrounding cellular reaction and few giant cells, epithelioid cells, or lymphocytes. Large numbers of organisms have sometimes been found in these lesions, and we have already mentioned the marked resemblance to the kind of acute caseating miliary tuberculosis produced experimentally by Rich (1944) by the injection of large doses of bacilli into the blood of over-sensitive animals. A further experimental parallel to the leukaemoid type of reaction is provided by the myelocytic-leukaemoid response in the blood of tuberculous rabbits given injections of tuberculin, a response presumably mediated by an allergic mechanism (Feldman and Stasney, 1937). Moreover, Sabin (1932) found that a striking multiplication of fibroblasts could be caused, both locally and diffusely, by an unsaponified higher-alcohol derivative of the waxes of tubercle bacilli, an observation which may be significant in the pathogenesis of tuberculous myelofibrosis. The hypoplastic changes in the marrow sometimes observed in tuberculous pancytopenia do not provide a basic contrast with the proliferative changes seen in leukaemoid and fibrotic reactions, since the border-line between reactive hyperplasia and exhaustion hypoplasia is ill-defined. Crail, Alt, and Nadler (1948) pointed out that tuberculous patients with myelosclerosis frequently show an initial marrow hyperplasia followed later by hypoplasia; the change from an active leukaemoid marrow, found at one stage during life, to a hypoplastic marrow shown at post-mortem examination, is illustrated by one of our cases (Case 4).

Our thanks are due to Sir Lionel Whitby (Cases 1 and 4) and Dr. Evan Jones (Case 3) for their help and for allowing us to describe patients under their care; to Dr. J. E. O'N. Gillespie for details and sections (Case 2); to Lieutenant-Colonel R. J. G. Morrison, R.A.M.C., for his valuable information about Case 1 before and after this patient was in Addenbrooke's Hospital; to Dr. A. M. Barrett for his histological reports; to Dr. A. J. N. Warrack for extracts from

his post-mortem report on Case 1; to Dr. J. L. Pinniger for much help and advice concerning the histological features in all the cases reported; and to Mr. A. E. Clark for the photomicrographs.

Summary

1. Four patients are described in whom pancytopenia in the peripheral blood was associated with miliary tuberculosis.

2. The histology of the miliary tubercles was atypical in that they consisted of miliary foci of necrosis with little cellular reaction. Acid-fast bacilli were seen in many of the lesions.

3. One case was diagnosed during life by aspiration liver biopsy, and the patient appears to have been satisfactorily treated with streptomycin and isoniazid up to the time of writing 18 months later.

4. The clinical features and the methods of diagnosis are discussed.

5. The question of the empirical treatment of patients who have aplastic anaemia with streptomycin and isoniazid is considered.

6. The pathogenesis of the histological lesions is discussed, with a remark on their similarity to the lesions produced experimentally by intravenous injection of tubercle bacilli into over-sensitive animals.

7. The pancytopenic blood picture is compared with the other haematological abnormalities sometimes associated with disseminated tuberculosis, including leukaemoid reactions, myelosclerosis, and polycythaemia rubra vera. It is postulated that all these reactions may have a similar underlying mechanism, just as the corresponding primary disorders are now thought to be examples of a single 'myeloproliferative syndrome', perhaps due to a factor stimulating the bone-marrow.

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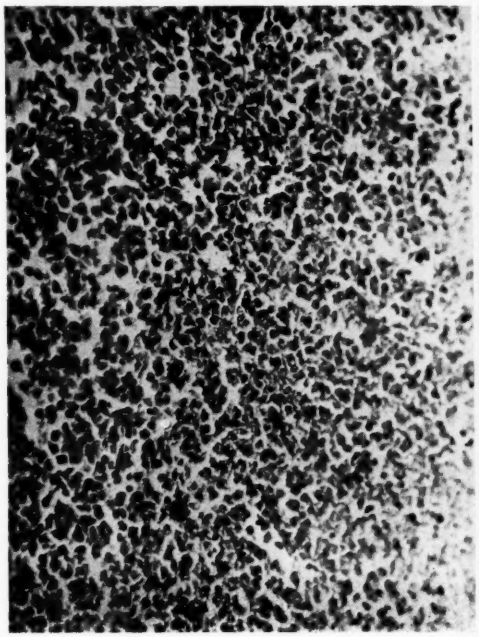

FIG. 1. Case 1. Liver. Focus of necrosis edged by a zone of chronic inflammatory cells (haematoxylin and eosin. × 240)

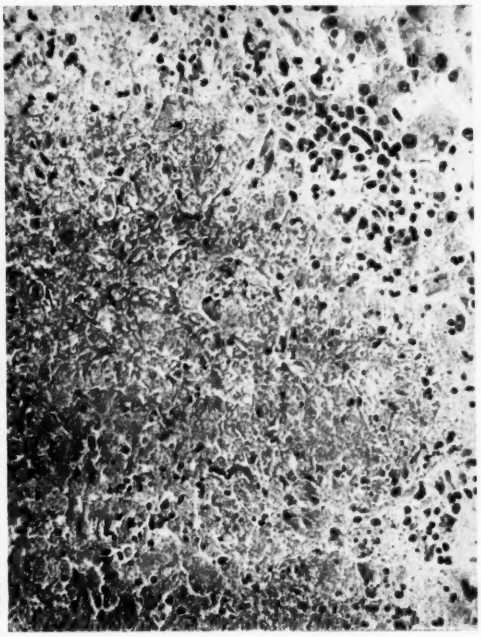

FIG. 2. Case 2. Liver. Focus of necrosis separated from normal liver by a narrow zone of chronic inflammatory cells (haematoxylin and eosin. × 240)

FIG. 3. Case 3. Liver. Typical tuberculous giant cells (haematoxylin and eosin. × 240)

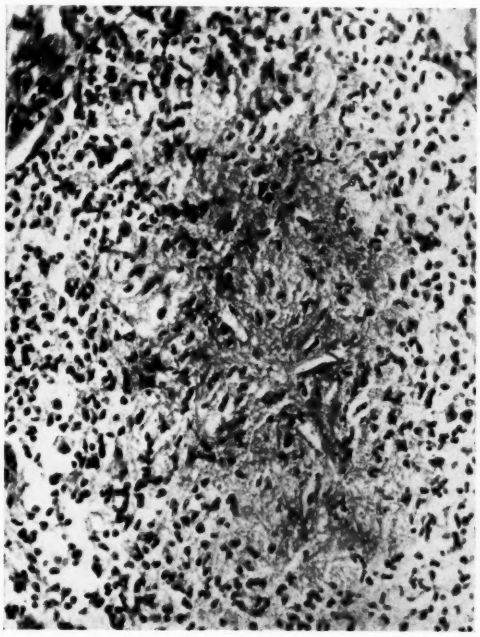

FIG. 4. Case 3. Liver. Focus of necrosis (haematoxylin and eosin. × 120)

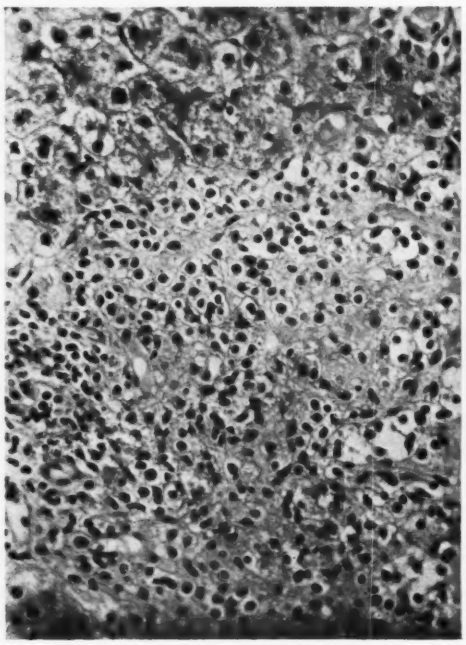

FIG. 5. Case 3. Liver, after treatment. Focus of fibrous replacement of liver cells (haematoxylin and eosin. × 240)

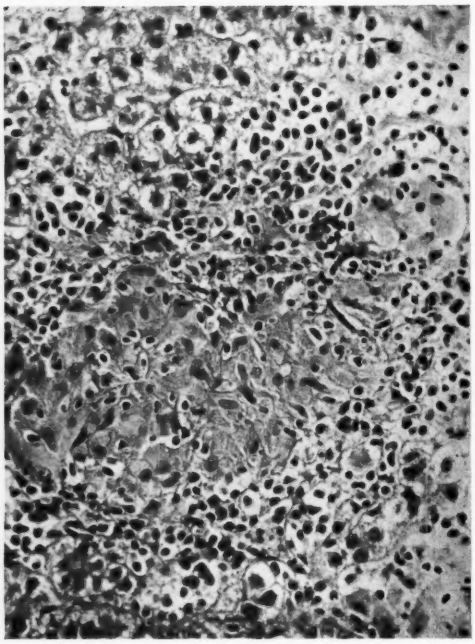

FIG. 6. Case 3. Liver, after treatment. Lesion resembling sarcoid granuloma (haematoxylin and eosin. × 240)

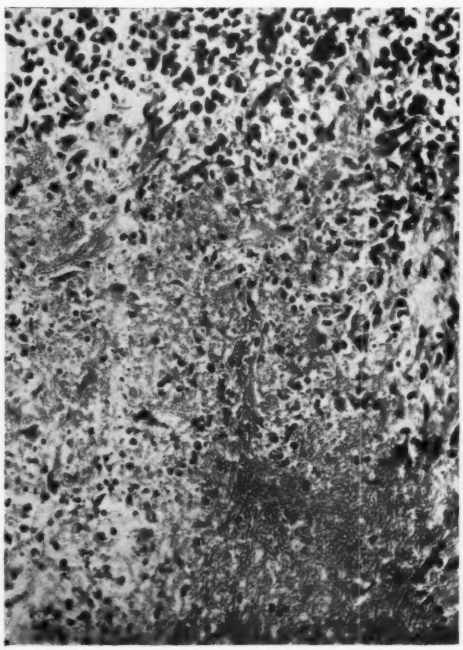

FIG. 7. Case 4. Lymph-gland. Necrotic lesion (haematoxylin and eosin. × 120)

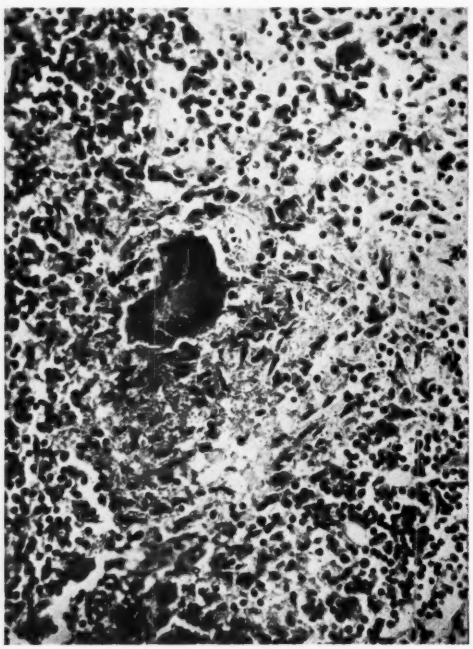

FIG. 8. Case 4. Lymph-gland. Typical tuberculous giant cell (haematoxylin and eosin. × 240)

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SPLENIC FUNCTION[1]

A Study of the Rationale and Results of Splenectomy in Blood Disorders

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The spleen can be removed with relative impunity and low mortality, and is not in any way essential to life. In practice splenectomy is often performed in haematological diseases, sometimes with remarkable success, sometimes with partial improvement in the clinical state, sometimes with no effect at all. It is fortunate that removal of the spleen, even if it does no good, rarely seems to do harm provided the operation is carried out gently and without haste, and provided that adhesions to the diaphragm are not an added complication. Nevertheless it is unsatisfactory to embark on an operation of this kind without some logical reason for its use and some confidence in the probable result. Published figures of the results of splenectomy in many conditions speak for themselves, but the reasons why improvement occurs in many and varied states of disease are far from agreed. Discussion of this problem involves consideration of the physiological functions of the spleen and their pathological abnormalities. The spleen, although still to a large extent the 'organ of mystery' of Galen's aphorism, is now known to be concerned with many physiological processes. These include the storage of blood and regulation of circulating blood-volume (at least in certain species), haemopoiesis at some phases of life, phagocytic and reticulo-endothelial activity, hormonal regulating influences, and antibody production. Clinical disorders involving defects of splenic function commonly result from the sum of several effects, and much less commonly from an isolated abnormality of a single splenic function. We shall therefore approach the problem of the rationale of splenectomy in blood diseases first by critically discussing the physiological background of splenic function. We shall then consider in turn the haematological disorders in which splenectomy may be of value, and attempt to assess the way in which disordered function of the spleen contributes to the process of disease, and how removal of this organ may lead to improvement. Illustrative examples of most of these disorders are taken from a group of about 40 patients who have been subjected to splenectomy while under our care during recent years.

Physiology of the Spleen

Reservoir function and the importance of red-cell sequestration. The vascular anatomy of the mammalian spleen is well adapted for the storage of blood diverted from the main stream of circulation. Knisely (1936*a*, *b*) demonstrated

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that blood from the Malpighian bodies passes through arterioles and arteriolar capillaries into venous sinuses, from which further circulation into collecting venules is controlled by an efferent sinus sphincter. The venous sinuses may act as normal conducting vessels, when they remain narrow and tube-like and the efferent sphincter is open. The sphincter may close, however, and this leads to gross distension of the venous sinus. The wall of the dilated sinus now acts as a filter which allows plasma to escape into the splenic pulp, while the erythrocytes are retained in increasing concentration. There is some uncertainty as to whether the sinus filter may allow passage of foreign particulate matter from the blood into the splenic pulp (Björkman, 1947), and it is possible that arterial blood may pass through the pulp in open drainage before entering the venous sinuses (MacKenzie, Whipple, and Wintersteiner, 1941), but Knisely's general description is now widely accepted. The whole subject of splenic circulation is extensively reviewed by Björkman (1947).

The splenic blood-storage mechanism might be expected to provide, in ordinary circumstances, a reservoir for blood which could be contributed to the circulation in time of need. In some animal species this certainly appears to be the case. Thus Barcroft and Barcroft (1923–4) found that in dogs and cats the spleen is capable of storing up to 20 per cent. of the blood-volume, so that with haemorrhage, exercise, excitement, or anoxia the spleen can contract and virtually bring about an auto-transfusion. The position in man is less clear. Ebert and Stead (1941) and Nylin (1947) have shown that the spleen in normal persons is of little or no importance as a reservoir, and that severe exertion does not lead to an increase in circulating red-cell mass. These observations do not deny the existence of a splenic storage mechanism in man, but they suggest that the stored red-cell concentrates are not used as an available reserve for maintaining or increasing the volume of blood in circulation. The process of plasma removal and red-cell concentration and sequestration by the splenic sinus filter may, however, be of primary physiological importance in man, because of the changes in trapped erythrocytes to which it gives rise. Bergenhem and Fåhraeus (1936) showed that the erythrocytes of incubated blood become spheroidal, probably as a result of the action of lysolecithin, a lytic substance which may be produced from serum lipids by lecithinase. This enzyme may also release lysolecithin from the lipids of many tissues, including the spleen, and the splenic sequestration of erythrocytes may allow such accumulated lysolecithin to act in high concentration. Moreover, the mere aggregation of red cells in packed masses may be followed by anoxic degenerative changes, with the production of metabolites possessing osmotic activity which tend to give rise to lysis. The studies of Selwyn and Dacie (1954) have made it clear that spontaneous autohaemolysis of red cells incubated *in vitro* is not a simple consequence of progressive swelling, since haemolysis increases during the second 24-hour period of incubation, when cell-volume is decreasing. They postulated a degenerative change in the cell-membrane as the factor of prime importance in lysis. Their experiments also cast some doubt on the importance of serum lysolecithin in producing red-cell lysis, since they were unable to show

any greater lytic activity of serum incubated for 24 hours as compared with fresh serum. The many and often conflicting observations concerning the influence of stasis in the spleen on normal erythrocytes have been reviewed by Ponder (1948). From the intricate complexities of the problem one can make the general conclusion that several mechanisms are potentially available in the spleen whereby erythrocytes may be made more spheroidal and the red-cell membrane weakened, whereupon haemolysis may ensue. But despite the existence of these mechanisms the spleen is not an important organ of red-cell destruction in normal circumstances, since, although splenectomy is followed by some decrease in faecal urobilinogen excretion, the operation does not lead to a significant increase in the life-span of erythrocytes (Singer and Weisz, 1945). Furthermore, after removal of the spleen the erythrocytes are found to be thinner and to possess increased osmotic resistance, and these changes may be due to the loss of splenic sphering activity (Singer, Miller, and Dameshek, 1941).

Haemopoietic function. It has long been known that from the second to the fifth month of foetal life the spleen is one of the main centres of blood formation, though activity in this respect has ceased by the time of birth. After birth, and throughout life, the spleen normally produces lymphocytes and monocytes, and only becomes a site of extramedullary haemopoiesis of myeloid type in pathological circumstances. The best-known example is the myeloid metaplasia which accompanies myelofibrosis.

Phagocytic and reticulo-endothelial activity. The spleen provides a major site for reticulo-endothelial activity. Foreign bodies such as Indian ink, blood parasites, and bacteria are readily ingested. Effete or dead cells and cell-fragments from the circulating blood are probably removed and digested by splenic macrophages and sinus-lining cells, but under normal circumstances it does not appear that splenic macrophages destroy active and functioning blood-cells of any kind.

Hormonal function. There is some experimental evidence for ascribing to the spleen a hormonal function active in regulating the maturation and release of red cells, leucocytes, and platelets from the marrow. In animals and man removal of the spleen is quickly followed by a very considerable increase in circulating leucocytes and platelets, which may persist for many weeks. Experimentally, it is instructive to note that in parabiotic animals no post-splenectomy leucocytosis occurs unless the spleen is also removed from the partner (Hirschfeld and Weinert, 1914). Cottier (1952) found that cytopenia and maturation defects of red- and white-cell precursors and megakaryocytes might follow the injection of certain splenic extracts. Further evidence of splenic influence on the release of red cells is provided by the unusual forms of erythrocytes, including showers of nucleated cells, and cells with Howell-Jolly bodies and Cabot rings, which appear in the circulation after splenectomy. Cruz and Robscheit-Robbins (1942) observed the effects of bleeding and of injections of acetyl-phenylhydrazine in dogs, comparing the results in those which had undergone splenectomy with those obtained in intact animals; they found that

in the animals subjected to splenectomy the numbers of normoblasts in the peripheral blood, in the first phases of the blood-regeneration period, were four times as great as in the others. Cruz and Robbins concluded that the results suggested a relationship between the function of the spleen and the maturation of the erythroblast in the bone-marrow, or 'a factor acting upon the launching mechanism of new red cells into the circulation'. Suggestive evidence of a hormonal relationship between the spleen and the bone-marrow is also provided by the experiments of Jacobson (1952), in which rats were protected from bone-marrow aplasia induced by X-rays if the spleen was exteriorized and shielded from irradiation. Some degree of protection was also achieved by the injection of cell-free splenic extracts at the time of exposure to X-rays.

Antibody-producing function. It is now certain that the spleen is a major site of antibody formation. The antibody response to injection of particulate antigens may be much lower in animals whose spleen has been removed than in controls; in suitable circumstances (Parker, 1937) antibodies are formed when splenic tissue is cultured *in vitro*; splenic-tissue slices have been shown to synthesize antibody (Ranney and London, 1951); and the abolition of antibody formation by X-rays may be prevented by spleen shielding (Jacobson, Robson, Marks, and Goldman, 1949). Whether reticulo-endothelial cells, lymphocytes, or plasma cells are primarily concerned in originating antibodies in the spleen and other sites is still undecided; perhaps all three cell-types participate in the response. It is sufficient for our present purposes to appreciate that the spleen occupies an important place among sites of antibody formation.

The Role of the Spleen and the Place of Splenectomy in Blood Disorders

Among the blood diseases in which splenectomy may be of value in treatment are certain well-defined conditions, usually diagnosed without difficulty, and a group of less clearly differentiated syndromes in which the diagnostic criteria are far from clear-cut. In the first group are hereditary spherocytosis (congenital haemolytic icterus or acholuric jaundice), idiopathic acquired haemolytic anaemia, and idiopathic thrombocytopenic purpura. The second group contains various disorders associated with peripheral cytopenia in which overactivity of some splenic function is thought to be responsible. These syndromes are often called hypersplenic, and are said to be primary or secondary according to whether they exist in the absence or presence of other demonstrable disease involving splenic enlargement.

Hereditary spherocytosis. This disorder, inherited as a Mendelian dominant, and characterized by fluctuating acholuric jaundice and anaemia with a tendency to aplastic crises, almost invariably responds in a striking way to splenectomy. The primary defect, however, is clearly not confined to splenic function, since many of the characteristic haematological abnormalities are still present, though usually to a less marked extent, after the spleen has been removed. This point is illustrated by the comparison, in Table I, of pre- and post-splenectomy haematological data in cases of hereditary spherocytosis

TABLE I

Pre- and Post-Splenectomy Haematological Data on 10 Patients with Hereditary Spherocytosis*

Patient	*Haemoglobin (gm./100 ml.)*		*Red cells (millions/ c.mm.)*		*Mean corpuscular volume (c.μ)*		*Mean corpuscular haemoglobin concentration (%)*		*Diameter-thickness ratio*		*% saline giving 5% haemolysis*		*Reticulocytes (%)*		*Serum-bilirubin (mg./100 ml.)*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
A. B.	7·9	15·2	3	5·1	76·6	80·3	33·9	37·3	2·2/1	2·7/1	0·7	0·55	13	0·9	1·2	0·3
T. E.	11	15·6	3·7	5·3	79	76	37·6	38·9	2·1/1	2·5/1	0·65	0·55	23	1·4	1·5	0·4
M. P.	9·8	14·8	3·4	5·1	82·1	83	35·1	35·3	2·1/1	2·7/1	0·7	0·55	26	0·7	2·5	0·8
P. T.	11·1	15	3·5	4·6	84·6	87·5	34·2	37	2·7/1	2·8/1	0·6	0·6	13	1·4	2·2	0·3
J. C.	11·7	14	3·8	4·7	89	86·5	37	35	2·0/1	2·6/1	0·7	0·55	23	0·5	1·7	0·4
B. H.	13·3	15·5	4·3	5·4	84	76	36·3	37·6	2·8/1	3/1	0·6	0·5	11	0·9	3·5	0·8
I. D.	8	13·4	2·2	4	97	90	37·9	37·6	2·2/1	3/1	0·8	0·6	29	4	2·1	0·5
H. C.	8·6	13·5	2·3	3·6	107	103	34·4	36·4	2·7/1	2·9/1	0·5	0·5	3	0·4	2·6	0·6
W. T.†	8	..	3·1	..	83	..	28	..	2·7/1	..	0·55	..	4	..	0·6	..
J. B.†	10·1	..	3·5	..	80	..	36	..	2·4/1	..	0·7	..	38	..	2·5	..

* The pre-splenectomy figures are averages of several estimations made usually during two or three weeks before operation; the post-splenectomy figures are averages of several estimations made between two months and three years after operation.

† Splenectomy was performed elsewhere in these two cases, and blood findings after operation are not available.

taken from our recent records. Haemoglobin and erythrocyte levels return to normal, while reticulocyte numbers and serum-bilirubin content are either normal or only very slightly increased. Mean corpuscular volume does not show any general tendency to increase or decrease, and mean corpuscular haemoglobin concentration remains at a high normal figure. The diameter-thickness ratio shows a consistent increase, with diminution in the degree of spherocytosis, and this finding is paralleled by an almost invariable decrease in saline osmotic fragility, which nevertheless continues outside the normal range.

All these observations on the effect of splenectomy in this disease are well substantiated by many published reports, amply reviewed by Dacie (1954*a*). The continued existence of a morphological abnormality in the red cells after splenectomy itself suggests that the primary disorder is one of red-cell structure rather than splenic malfunction, but much more convincing evidence on this matter is now available. Studies of red-cell survival (Dacie and Mollison, 1943) have shown that normal erythrocytes, transfused to patients with hereditary spherocytosis, remained in the circulation for a normal life span, while the patients' spherocytes were rapidly destroyed in a normal recipient. The role of the spleen in the removal and destruction of spherocytes, suggested by the effects of splenectomy, is clearly demonstrated by the greatly enhanced survival of spherocytes when transfused into normal recipients in whom the spleen has been removed (Schrumpf, 1951). Present concepts of the pathogenesis of this disease therefore postulate a fundamental defect in erythrocyte architecture and enzymatic constitution, probably involving abnormalities of carbohydrate metabolism, particularly glycolytic reactions (Prankerd, Altman, and Young, 1954; Young, 1955), leading to the formation of deformed, spherocytic red cells, and the selective destruction of such cells by the spleen. Since the spleen of normal individuals exerts a similar destructive activity against transfused spherocytes, it appears that normal splenic functions alone are sufficient to account for spherocyte destruction. Among the physiological functions of the spleen discussed earlier, that of red-cell sequestration and concentration in splenic sinuses, with consequent increase in sphering and tendency to lysis, together with the phagocytic reticulo-endothelial activity of sinus-lining cells and pulp macrophages, seems to provide a suitable mechanism which, though normally of little importance in red-cell destruction, might selectively destroy erythrocytes already suffering from an intrinsic structural weakness. There is, indeed, experimental evidence that spherocytes are sequestrated in the spleen more readily than normal red cells (Emerson, Shen, and Castle, 1946; Young, Platzer, Ervin, and Izzo, 1951). It appears probable that phagocytosis of intact erythrocytes in the spleen does not play much part in this disorder, since it is not a histological feature, but the splenic macrophages are commonly found to be heavily laden with haemosiderin, and the 'graveyard' function of the organ is clearly being considerably exercised. In sections from the excised spleen congestion with erythrocytes is conspicuous, and these are principally found in the pulp rather than in the sinuses. Attention has already been drawn to the differences of opinion as to the existence of a closed or open splenic vascular

pattern. Knisely and the proponents of closed circulation believe that in life the cell sequestration occurs in the sinuses, and that the congested pulp and empty sinuses in sections of excised spleen represent an agonal change. Gripwall (1938) found the sinuses distended with erythrocytes in rapidly fixed splenic tissue removed at operation, and Dean (1953) noted that in the majority of 13 cases of hereditary spherocytosis, in which he examined the spleen after operation, there was the commonly recorded congestion of the pulp, with compression of the sinuses, in the body of the organ, but in areas under the capsule the sinuses were swollen and engorged with blood and the pulp-cords much smaller. The question whether in life the congestion is predominantly in sinuses or in the pulp must be regarded as unsettled, but in any case it is clear that a mechanism exists for selective retention and destruction of spherocytes. Lysolecithin activity, present in the normal spleen, may assume greater importance in this disease, since Scheff and Awny (1949) have shown that the spleen in congenital haemolytic icterus has increased lecithinase activity, with greater production of lysolecithin, and furthermore the spherocyte is more susceptible to lysis by lysolecithin than a normal erythrocyte. It is doubtful, however, whether this increased lysolecithin activity should be regarded as a primary splenic malfunction, since it can be explained as a consequence of excessive blood stasis.

Idiopathic acquired haemolytic anaemia. This disease, which may occur in acute, subacute, or chronic forms, is associated with the presence of a circulating antibody, active at 37° C., though in a small proportion of cases activity only occurs when blood in some part of the circulation is chilled below the normal temperature. The antibodies concerned are auto-antibodies to which the patient's erythrocytes are susceptible. Red cells from patients with this disease can be shown by the antiglobulin test to be coated with antibody, whose existence in the plasma also can be shown by indirect antiglobulin tests or the use of enzyme-treated cells. The studies of Dacie and Mollison (1943), Brown, Hayward, Powell, and Witts (1944), Loutit and Mollison (1946), and Mollison (1947), demonstrated that in such patients transfused normal red cells are rapidly eliminated, and Selwyn and Hackett (1949) showed that prior to their elimination the normal corpuscles may also become coated with antibody, and so react with antiglobulin serum. The red cells of the patient, on the other hand, are eliminated from the circulation of a normal recipient at a normal rate, apart from an initial phase of increased destruction, and this finding suggests that some elution of the sensitizing antibody may take place in the recipient's circulation. Indeed, Selwyn and Hackett suggested that transference of antibody to the recipient's corpuscles may take place in such transfusion experiments, since both the recipient's and the donor's erythrocytes may be agglutinated by antiglobulin serum, although the sensitization is not intense enough to lead to increased cell destruction. It certainly seems reasonable to suppose that the presence of auto-antibody in this disease plays an important part in the pathogenesis of haemolysis, but antibodies capable of provoking *in vitro* haemolysis can hardly ever be demonstrated. The process is clearly not a simple one, and a great deal of work has been published both on the serological aspects

and on the pathogenetic mechanisms involved. The problem with which we are at present concerned, however, is that of the role of the spleen in this disorder. Splenectomy is successful in improving the condition substantially, or even in producing a clinical cure, in about 50 per cent. of cases.

Case reports of splenectomy in idiopathic acquired haemolytic anaemia

1. *R. B., a woman aged 24 years. Clinical history.* She was admitted to hospital in October 1948, with a history of increasing lassitude and palpitations on exertion for a month. There was obvious pallor, marked tachycardia, orthopnoea, and a faintly icteric tinge in the conjunctivae. Fever ranged between 99° and 101° F. Haemoglobin was found to be 3·6 gm. per 100 ml., and reticulocytes 15 per cent. Transfusions were followed by a rapid fall in the haemoglobin level, and neither penicillin nor intramuscular anahaemin influenced the course of the disease. At this stage the patient was transferred to Addenbrooke's Hospital under our care. The spleen could be felt, but the physical signs were otherwise unchanged. There was no glandular enlargement. A blood count showed a macrocytic anaemia of moderate severity, with haemoglobin 6·9 gm. per 100 ml., mean corpuscular volume 112 c.μ, reticulocytes 30 per cent., and serum-bilirubin 2·3 mg. per 100 ml. The stained smears showed obvious spherocytosis, the erythrocyte osmotic fragility was markedly increased, the direct Coombs test was strongly positive, and weak cold auto-agglutinins were present. There was nothing suggestive of familial anaemia or icterus in the family history, and examinations of the blood of both parents gave no evidence of haemolytic anaemia or spherocytosis. The patient's serum contained an auto-antibody which sensitized the cells of three of 10 donors' blood of the same group (O, Rh-positive), but both sensitized and unsensitized cells showed similar genotypes. Since the haemoglobin level continued to fall at a rate of about 0·4 gm. per 100 ml. per day, blood transfusion was carried out with cells which were not sensitized by the patient's serum *in vitro*, and splenectomy was performed on November 18, 1948. The spleen was considerably enlarged ($19 \times 11 \times 7{\cdot}5$ cm.; weight 835 gm.), and was associated with five splenunculi. After splenectomy there was a temporary fall in the reticulocytosis, and a slow decline in serum-bilirubin to 1·5 mg. per 100 ml. three weeks after operation. The haemoglobin continued to fall, but at a reduced rate, and slight fever persisted until mid-January. From this time onward a steady and remarkable improvement ensued, and in October 1949 the haemoglobin had risen spontaneously to 12·8 gm. per 100 ml., reticulocytes were 0·5 per cent., the direct Coombs test was only weakly positive, and the serum-bilirubin 0·4 mg. per 100 ml. This excellent progress was maintained, and in June 1950 the haemoglobin level was 14·0 gm. per 100 ml., the erythrocytes showed scarcely perceptible agglutination in an antiglobulin-serum titration, and the patient was clinically quite well.

Spleen histology. Sections, examined by Dr. A. M. Barrett, were reported to show much haemosiderosis and much extramedullary haemopoiesis; there were numerous clusters of immature red cells in all stages of development, and occasional myelocytes and megakaryocytes. Late normoblasts were very scanty compared with the number of more primitive red cells. In some places the most mature of the nucleated red cells present appeared to be undergoing haemolysis, whereas fully developed erythrocytes nearby showed no evidence of haemolysis. The sinusoids were engorged, but the pulp contained relatively few red cells. Many of the Malpighian bodies had Flemming centres, and in a few there was fibrinoid degeneration. Plasma cells were abnormally abundant, especially around small arteries and fibrous septa. This histological picture was unlike

that usually seen in hereditary spherocytosis, and the extent of myeloid metaplasia was greater than commonly encountered in acquired haemolytic anaemia.

2. *C. F., a man aged 18 years. Clinical history.* Apart from childhood diseases, this patient was healthy until the first week of October 1949, when headache and general malaise began, becoming rapidly more severe. The urine was noticed to be reddish in colour and very dark. By October 6 he could not stand up without fainting. He was admitted to Bedford County Hospital on October 7, given a transfusion of two pints of blood, and transferred to Addenbrooke's Hospital under our care on October 10. At this time he was extremely pale, with slight jaundice of the skin and conjunctivae, but showed no petechiae or ecchymoses of the skin or mucosae. There was gingivitis, but the gums were not spongy; there was no significant glandular enlargement, and the spleen and liver could not be felt. The urine was dark red in colour, and showed haemoglobin and methaemoglobin spectroscopically. The haemoglobin was 3·3 gm. per 100 ml., mean corpuscular volume 97 c.μ, mean corpuscular haemoglobin concentration 37·1 per cent., mean corpuscular average thickness 3·9μ, mean corpuscular diameter (Price–Jones curve) 5·6μ, and diameter-thickness ratio 1·4:1. Erythrocyte osmotic fragility was grossly abnormal, commencing in 0·8 per cent. saline and virtually complete in 0·5 per cent. saline. The direct antiglobulin test was strongly positive, reticulocytes 34 per cent., and serum-bilirubin 2·9 mg. per 100 ml. There was a leucocytosis of 32,000 per c.mm., with considerable shift to the left in the granulocyte series, and a normoblastosis of 27,500 per c.mm. Transfusion was a matter of urgency, and three pints of Group O, Rh-positive blood were given at a rapid rate, followed two days later by a further four pints of packed cells. The haemoglobinuria lessened, and had ceased by October 17, but extensive haemolysis continued; the serum-bilirubin persisted between 2 and 3 mg. per 100 ml., reticulocytes remained between 18 and 40 per cent., and the rate of haemoglobin decrease was more than 2 gm. per 100 ml. per day. The leucocytosis and normoblastosis, however, greatly diminished. On October 19 splenectomy was performed, a total of five pints of packed cells being given during the day. A remarkable and immediate improvement in the haemolytic process took place after the operation; there was a steady rise in the haemoglobin level, with a decrease of reticulocytes and serum-bilirubin concentration. By December 12 the haemoglobin was 15·6 gm. per 100 ml., reticulocytes 1·1 per cent., and serum-bilirubin 0·2 mg. per 100 ml., and the leucocyte count was within normal limits. At this stage the mean corpuscular diameter was 7·1μ, mean corpuscular average thickness 2·3μ, and diameter-thickness ratio 3·1:1, and the Coombs test had become negative. Clinical recovery was full and uninterrupted.

Spleen histology. The spleen, which was only moderately enlarged (weight 450 gm.), appeared intensely congested to the naked eye. Sections, examined by Dr. J. H. Dean, were reported to show gross engorgement of the pulp with blood, while the sinusoids were relatively empty. Many of the reticulum cells of the pulp were impregnated with haemosiderin, and there was diffuse iron-staining of the cytoplasm of many littoral cells lining the sinuses. The Malpighian bodies appeared normal, but were conspicuous by contrast with the engorged pulp. Flemming centres were present, and there was evidence of reactive hyperplasia. There were occasional islands of normoblastic erythropoiesis in the pulp, and a few megakaryocytes and neutrophil myelocytes were seen. This general histological picture is of a pattern commonly seen in acquired haemolytic anaemia.

3. *I. C., a woman aged 51 years. Clinical history.* This patient gave a history of increasing dyspnoea, weakness, and pallor, and fluctuating jaundice, for 10 weeks. She had noticed that the urine was dark for a month before her admission to hospital on August 12, 1948. There was no family history of anaemia or jaundice, nor had the patient previously had any such illness. Apart from pallor and moderate jaundice, the only abnormal physical sign at this time was a just palpable enlargement of the spleen. Blood examination showed haemoglobin 6·3 gm. per 100 ml., mean corpuscular volume 130 c.μ, mean corpuscular haemoglobin concentration 30 per cent., reticulocytes 62 per cent., mean corpuscular diameter 6·5μ, mean corpuscular average thickness 3·9μ, diameter-thickness ratio 1·7:1, serum-bilirubin 3·6 mg. per 100 ml., and erythrocyte osmotic fragility considerably increased; the Coombs test, both direct and indirect, was strongly positive. The leucocyte count was within normal limits, and an occasional late normoblast was present in the peripheral blood. There was no sign of remission in the haemolytic process after seven weeks' observation, although the haemoglobin level remained fairly constantly in the neighbourhood of 6 gm. per 100 ml. Transfusion of compatible blood not sensitized *in vitro* by the patient's serum was successful in raising the haemoglobin level to 8·8 gm. per 100 ml., and splenectomy was then carried out on September 30. The operation was followed by immediate amelioration of the haemolytic process, and a gradual increase in haemoglobin ensued, accompanied by a decrease in reticulocytes and serum-bilirubin. By January 7, 1949 the haemoglobin had risen to 13·6 gm. per 100 ml., with the mean corpuscular volume 91 c.μ, mean corpuscular haemoglobin concentration 37·5 per cent., mean corpuscular diameter 6·0μ, mean corpuscular average thickness 3·3μ, and diameter-thickness ratio 1·8:1. The persistent spherocytosis was associated with a persistently and grossly increased osmotic fragility, but the reticulocytes were now only 1·2 per cent., and serum-bilirubin 1·0 mg. per 100 ml. The direct Coombs test was still strongly positive. Clinical progress was excellent, with a steady return to full health and activity. Observation was continued at intervals, and there was further slow improvement in the haematological features. Eighteen months after operation the Coombs test became negative, and at this time the haemoglobin level was 15·4 gm. per 100 ml., mean corpuscular volume 83 c.μ, and mean corpuscular haemoglobin concentration 37·0 per cent. Spherocytosis was less marked, the diameter-thickness ratio now being 2·5:1, but the osmotic fragility was still much increased. The reticulocytes were 0·8 per cent., and serum-bilirubin 0·7 mg. per 100 ml. Clinically the cure appeared to be complete.

Spleen histology. The spleen was only slightly enlarged, weighing 172 gm., and showed obvious congestion. Sections were reported by Dr. A. M. Barrett to show abundant red cells in the pulp, with evidence of haemolysis of blood subsequent to the operation. The Malpighian bodies were of medium size, and some showed Flemming centres, occasionally with fibrinoid degeneration. A moderate amount of haemosiderin was present, mostly in reticulum cells in the pulp. No islands of myeloid metaplasia were seen, and there was little if any reticulum-cell hyperplasia. The general histological picture was of a kind seen commonly both in hereditary spherocytosis and in idiopathic acquired haemolytic anaemia.

The major questions arising when splenectomy is considered in this disease are, first, what part does the spleen play in producing the syndrome, and second, why is the operation sometimes effective and sometimes not? A number of splenic functions may here be of importance, either through a primary func-

tional derangement or through the exercise of a normal physiological mechanism on unduly susceptible cells. The antibody-forming capacity of the spleen at once suggests the possibility that this organ might be a major site for production of the auto-antibodies of acquired haemolytic anaemia. Controversy exists over the causes of antibody formation in this disease. The mechanism of immunization, though a protective one adapted to neutralize, destroy, or eliminate proteins which are foreign and therefore noxious to the body, and though accurately predictable so far as a quantitative antibody-response is concerned, is not apparently capable of exercising a qualitative distinction between various kinds of noxiousness or 'foreignness'. Hence it may come about that autogenous blood-cells of all kinds, when slightly altered by a damaging contact with some drug, viral or bacterial enzyme, or other extraneous substance, are sufficiently altered to set in motion a process of auto-immunization, giving rise to antibodies destructive to the particular blood-cell concerned. That acquired haemolytic anaemia arises as a clinical manifestation of such a process is possible, though not proven. The work of Dodd, Wright, Baxter, Bouroncle, Bunner, and Winn (1953) showed that both trypsinized erythrocytes and erythrocytes from many cases of this disease are immunologically different from normal erythrocytes, but whether the apparent modification of surface antigenic structure is a cause of antibody formation or a result of antibody activity must be regarded as uncertain. Alternatively the so-called 'auto-antibodies' may be produced, not as a specific reaction to a modified erythrocyte-antigenic system, but as a result of primary abnormality of the plasma-protein and antibody-forming mechanism. This would better explain the wide range of activity and lack of specificity of such antibodies in most cases. Dacie (1954*b*) gave an excellent discussion of these hypotheses and other possible contributory factors. Splenectomy is sometimes followed by a sharp reduction in the level of auto-antibody, as in the two cases described by Evans and Duane (1949), but in other patients the reduction may be slight, or may not take place at all (Dacie, 1954*b*). The variation in response in this respect is illustrated also in the three case reports presented above. It seems fair to conclude that in some cases, and perhaps in all, the spleen is a site of auto-antibody elaboration, but not the only site, and, moreover, that a further splenic function is also involved in the genesis of haemolysis. This additional mechanism is probably that of cell sequestration and concentration in splenic sinuses, with the consequent tendency to haemolysis already discussed. Such a process would be exacerbated in acquired haemolytic anaemia, since the normal course of cell retention in the venous sinuses would be supplemented by erythrocyte agglutination due to the action of auto-antibodies. Sequestration may also lead to spherocytosis, which is a definite feature in some cases, and experience tends to show that when this phenomenon is conspicuous the outlook for patients after splenectomy is good (Whitby, 1952). Active disposal of erythrocyte fragments by splenic reticuloendothelial cells provides the final stage in red-cell destruction. The histology of the excised spleen is much less uniform than in hereditary spherocytosis, and the case records given above illustrate the variability of the findings; but

congestion and haemosiderosis are usually prominent, and suggest that erythrostatic and phagocytic activity must be considerable. This combination of splenic activities offers a reasonable explanation of those factors in pathogenesis which might be removed by splenectomy, and therefore provides a rational basis for operation. We are left with the problem of those cases which fail to respond to splenectomy. There is no clear answer at present to this difficulty, but, since the spleen is not the only site of antibody formation or red-cell destruction, one may suppose that in unresponsive cases the extrasplenic contribution to these processes bulks particularly large. Unfortunately neither the clinical nor the laboratory features in a particular case, nor the response to cortisone or corticotrophin, supply information of assistance in deciding whether splenectomy is likely to succeed or fail.

Idiopathic thrombocytopenic purpura. Thrombocytopenic purpura unassociated with any concurrent disease such as aplastic anaemia, leukaemia, congestive splenomegaly, lymphadenoma, or carcinomatosis was regarded until recent years as a single 'idiopathic' entity. The term 'idiopathic' or 'essential' thrombocytopenic purpura (I.T.P.) is still conveniently retained to cover this group of clinically similar states, although it has become clear that the syndrome may have a number of causative factors and differing modes of pathogenesis. Among these factors must now be included certain bacterial and viral infections, and ingestion of various chemicals and drugs. Some authorities, such as Harrington (1954), rigidly exclude from the heading of idiopathic thrombocytopenic purpura any cases in which 'drug, infection, or other potential inciting mechanism seems plausible', but such a dividing line is difficult to draw, since causative factors may often exist when they are not suspected, or be suspected when they are not in fact operative, and it may be impossible to confirm or refute such suspicions by laboratory investigations. It therefore seems reasonable at the present time to use the name I.T.P. in a wide sense, with the appreciation that a clear subdivision on a basis of aetiology may soon be forthcoming.

The clinical features of this disease enable a distinction to be drawn between acute, frequently self-limited, forms of I.T.P. and chronic, persistent, episodic types. Hirsch and Dameshek (1951), from an analysis of 89 cases, sharply differentiated the two forms of this disorder. In the acute form the incidence is equal in both sexes, there is no past history of bruising or haemorrhagic tendency, the patient usually presents an obvious purpura, there is commonly lymphocytosis and eosinophilia of blood or bone-marrow, drug-exposure or infection has often taken place recently, and the disease spontaneously ceases after a course of three or four months. Repeated attacks do not occur. The spleen is not usually palpably enlarged. In chronic I.T.P. there is a predominance of the disease in female subjects, a past history of increased bleeding or bruising tendency is almost invariable, the presenting symptom is frequently bleeding from mucous membranes, such as the uterine mucosa, rather than frank purpura, an increase of lymphocytes and eosinophils in the blood or marrow is not common, there is no known relationship to previous drugs or infections,

and the disease pursues a fluctuating, chronic course, with spontaneous partial remissions and exacerbations. The spleen is palpable in about 10 per cent. of this group of patients. The differentiation of these two kinds of I.T.P. is by no means invariably as sharp as the analysis of Hirsch and Dameshek might lead one to suppose. Patients presenting syndromes fairly typical of acute I.T.P. may progress to a chronic form of the disease (see Case 9) or may suffer relapses (Evans, 1955), but in general the distinction is both valid and valuable.

Splenectomy is not indicated in the acute cases unless control by platelet-rich blood transfusion and cortisone proves ineffective, especially since the operative risk in acute severe purpura is far from negligible; but if the spleen is removed successfully the duration of the disease may be curtailed. Brief case reports of three patients with acute thrombocytopenic purpura, one of unknown aetiology and the others associated respectively with an acute infectious fever and a drug sensitivity, are given below.

4. *A. B., a man aged* 37 *years*, had been quite healthy until March 1952, when spontaneous bruising and purpuric spots on the arms and shoulders appeared. There was a severe epistaxis, and submucous haemorrhages were observed in the mouth. Apart from the haemorrhagic signs physical examination was negative. The spleen could not be felt. The condition persisted for eight weeks without either improvement or severe exacerbation, and he was admitted to hospital under our care on May 1. Investigations at this time showed a strongly positive capillary-resistance test, bleeding time between eight and 20 minutes on several occasions, and platelet counts persistently very low, ranging from 40,000 to 60,000 per c.mm. There was no anaemia, and the leucocyte picture was normal. A sternal puncture on May 7 showed an active cellular marrow with a slightly increased megakaryocyte content. The cytoplasm of the megakaryocytes was only faintly granular, and showed no coarse particles or peripheral platelet formation. The marrow contained about 6 per cent. eosinophile polymorphs and eosinophil-precursors. Splenectomy was performed on May 14. Immediately before operation the bleeding time was eight minutes, but when the splenic artery was tied the bleeding time fell at once to three minutes. There was no significant difference in cellular content and platelet count between splenic arterial and venous blood samples. A second sternal-marrow sample was aspirated within 20 minutes of the operation and, while the differential count showed no considerable difference from the previous specimen, the megakaryocytes showed definitely coarser cytoplasmic granularity, although there were still no peripheral platelets to be seen. On May 15 the platelet count had risen to 290,000, on May 17 to 600,000, and on May 20 to 860,000 per c.mm.; a third sternal-marrow aspirate on May 21 showed enormous numbers of platelets being formed at the periphery of megakaryocytes. After the operation the capillary resistance test became negative, and the bleeding time remained below three minutes. A month later, on June 21, the thrombocytes numbered 880,000 per c.mm., and complete clinical recovery had taken place. There has been no subsequent relapse.

5. *R. R., a boy aged two years.* A month after recovery from an exanthematous fever, probably measles, there was a sudden onset of extensive bruising following minor injury or spontaneously, together with some bleeding from the gums. There were no swelling of the joints, urticaria, or other anaphylactoid signs, but a generalized petechial rash with many discoloured ecchymoses was present.

The spleen could not be felt, and there was no glandular enlargement. The blood count revealed marked thrombocytopenia (56,000 per c.mm.). The haemoglobin level and leucocyte count were normal for a child of this age. The bleeding time was 32 minutes, and the tourniquet test strongly positive. The tibial marrow was normally cellular, and there was no increase of eosinophils, but the megakaryocytes did not show peripheral platelet formation, and were poorly granular. Conservative measures were advised when this patient was seen by us in the haematology clinic two weeks after the onset, since some amelioration was already noticed by the parents, and without the assistance of transfusion, steroid hormones, or splenectomy the patient made a full clinical recovery. Further blood counts could not, unfortunately, be obtained.

6. *A. D., a man aged 54 years,* presented an erythematous, petechial, and purpuric rash on the trunk and limbs, which had come on suddenly three weeks previously. There were no other relevant physical abnormalities, but the tourniquet test was strongly positive, the platelet count was 130,000 per c.mm., and clot retraction and prothrombin consumption were markedly defective. For two or three months before the onset he had been taking sleeping tablets which contained carbromal and bromvaletone, and the serum was found to contain an antibody reacting with normal platelet suspensions in the presence of these drugs. The tablets were discontinued, and a rapid complete recovery ensued.

In chronic I.T.P. splenectomy leads to complete remission in over 70 per cent. of cases (Elliott and Turner, 1951), and undoubtedly is the treatment of choice. Our present series of patients who have had splenectomy includes four with chronic I.T.P., in all of whom a complete clinical cure has been induced. Case histories of these patients are typical and unremarkable, and are therefore given in very brief outline. Each patient was followed up for a year after operation, and was then asked to report any later recurrence of bleeding. None has done so, and it is probably fair to conclude that so far no relapse has occurred.

7. *M. L., a woman aged 26 years.* Date of splenectomy October 1948. This patient presented with a complaint of heavy menstrual loss and easy bruising, and gave a history of excessive bruising and a tendency to considerable bleeding after minor trauma for the previous 12 years. There was a mild haemorrhagic anaemia, with a normal leucocyte count, and the platelets numbered 70,000 per c.mm. The bleeding time was over 20 minutes (Duke's method), and the tourniquet test was positive. Splenectomy produced an excellent response, the bleeding time returning to normal, the platelet count rising to 600,000 per c.mm. and remaining within the normal range, and menstrual loss becoming normal.

8. *M. C., a woman aged 20 years.* Date of splenectomy November 1953. There was a year's history of repeated epistaxis, bruising on the legs and arms, and menorrhagia. More recently a fine purpuric rash had developed on the legs and shoulders. The spleen was not palpable. Haemoglobin was 8·4 gm. per 100 ml., with mean corpuscular haemoglobin concentration 31 per cent.; the leucocytes were normal, and platelets numbered 36,000 per c.mm. Clot retraction and prothrombin consumption showed marked deficiency, the tourniquet test was strongly positive, and marrow aspirates contained many immature, non-granular megakaryocytes. Splenectomy was followed by a rapid and sustained increase of platelets to between 220,000 and 300,000 per c.mm., the tourniquet test became negative, and there was cessation of haemorrhagic symptoms and signs. The haemoglobin level rose to over 13 gm. per 100 ml.

9. *B. T., a boy aged eight years.* Date of splenectomy May 1954. This child was seen on account of epistaxis, bruising of the legs, and a generalized fine purpuric rash over the trunk and arms, which had developed progressively for three weeks. The spleen was not palpable. A positive tourniquet test was found, and platelets numbered 50,000 per c.mm., with parallel defects in prothrombin consumption and clot retraction. He was treated with corticotrophin initially, and during the next two months there was clinical improvement, but no increase of platelets. Corticotrophin was discontinued without a clinical relapse, but the persistence of severe thrombocytopenia, and occasional minor recurrences of bruising and petechiae, for the next six months, showed that the condition had become chronic I.T.P. Marrow examination before operation showed many agranular megakaryocytes, and at this time the platelet count was 30,000 per c.mm. Splenectomy led to immediate improvement; the platelets increased to 720,000 per c.mm., and the tourniquet test became negative. There has been no further clinical relapse, and the platelet count remains over 500,000 per c.mm.

Histology of the spleen in idiopathic thrombocytopenic purpura. There is remarkably little histological abnormality in spleens from either acute or chronic I.T.P., and the spleens from the patients discussed above had no diagnostic or characteristic features. Most showed slight reactive hyperplasia and pulp congestion, and a tendency to reticulum-cell hyperplasia of minor degree. No identifiable megakaryocytes or platelets could be seen.

The role of the spleen in I.T.P. has been the subject of extensive conjecture since 1916, when Kaznelson first reported the successful effect of splenectomy, and it is still far from clear. Until very recently there were two chief schools of thought in this matter, the one believing that excessive destruction of platelets took place in the spleen in this disease, the other that the spleen exercised an inhibitory action on the maturation of megakaryocytes, and on platelet formation in, and release from, the bone-marrow. Both these hypotheses assigned the primary abnormality to the spleen. The first theory, that of excessive splenic thrombocytolysis, was originally suggested by Kaznelson, and later supported principally by Doan and Wiseman and their associates. Histological evidence of increased platelet sequestration and destruction in the spleens of I.T.P. is not usually found, although Nickerson and Sunderland (1937) and Wiseman, Doan, and Wilson (1940) claimed to observe phagocytosis of platelets by splenic macrophages. Studies of splenic activity *in vivo* have given discrepant results, Stefanini, Chatterjea, Dameshek, Welch, and Swenson (1952) claiming that no selective sequestration and destruction of platelets takes place, at least in acute I.T.P., while Wright, Doan, Bouroncle, and Zollinger (1951) offered evidence to the contrary in the cases of I.T.P. which they studied. The second hypothesis, that of marrow inhibition by some splenic product, arose from the early observations of Frank (1915, 1925), later confirmed by many authorities (Klima, 1938; Limarzi and Schleicher, 1940; Dameshek and Miller, 1946), that marrow megakaryocytes were normal or increased in numbers in I.T.P., but showed defective granularity and platelet formation. After splenectomy a rapid change occurred in the marrow, and megakaryocytes could be seen surrounded by huge masses of platelets. We have already reviewed some of the evidence supporting the concept of splenic hormonal activity, and in many ways

the concept is an attractive one. Nevertheless the existence of a splenic hormone lacks direct experimental support, since the injection into animals of extracts from normal and pathological spleens, while commonly producing some fall in platelet numbers, has given inconsistent and equivocal results (Troland and Lee, 1938; Tocantins, 1939; Pohle and Meyer, 1939; Hobson and Witts, 1940; Rose and Boyer, 1941; Paul, 1941–2; Cronkite, 1944; Singer and Rotter, 1949). Emphasis has now turned from these two opposing doctrines to a third hypothesis, more firmly grounded in experimental study and observation, and perhaps providing a synthesis of ideas in which the earlier schools of thought may be incorporated. This is the concept of auto-immune I.T.P., which parallels that of auto-immune acquired haemolytic anaemia. Many patients with I.T.P., both acute and chronic, have a thrombocytopenic factor in their plasma, often demonstrable *in vitro* as a platelet agglutinin (Evans, Takahashi, Duane, Payne, and Liu, 1951; Harrington, Hollingsworth, Minnich, and Moore, 1951; Harrington, Minnich, Hollingsworth, and Moore, 1951; Dausset, Delafontaine, and Fleuriot, 1952; Stefanini, Chatterjea, and Adelson, 1952; Sprague, Harrington, Lange, and Shapleigh, 1952; Kissmeyer-Nielsen, 1953; Tutein, Hoorweg, and van Loghem, 1953). Harrington (1954), using a sensitive technique for the detection of platelet agglutinins, found them present in the sera of roughly two-thirds of his series of 72 patients in whom acute or chronic I.T.P. was apparently not associated with any potential inciting mechanism. Study of the patients from his series who underwent splenectomy suggests that subjects with positive auto-agglutinin reactions respond much better than those whose reaction is negative. Among 38 'positive' patients 25 had complete remissions after splenectomy, while only four of 16 'negative' patients enjoyed complete remissions. Stefanini (1955) had not been able to substantiate these results from his experience, but, despite the use of various techniques in his laboratories, platelet agglutinins could be detected in only about 30 per cent. of his cases. Evidence that the existence of an agglutinating antibody can explain the full clinical and laboratory picture of I.T.P. is given by the observations of Dausset, Delafontaine, and Fleuriot (1952), Harrington, Sprague, Minnich, Moore, Aulvin, and Dubach (1953), Miescher, Vannotti, Cruchaud, and Hemmeler (1952), and Stefanini, Dameshek, Chatterjea, Adelson, and Mednicoff (1953). They found that the administration of plasma from a patient with auto-immune I.T.P. to a normal recipient led not only to marked peripheral thrombocytopenia and skin purpura, but also to degenerative changes, loss of granularity, and failure of platelet formation in the bone-marrow megakaryocytes. The decline in numbers of platelets was too fast to be explained by defective formation alone, and thrombocytolysis was clearly also taking place in these experiments.

If we now try to visualize the part played by splenic activities in this complicated picture, it seems probable that the situation is closely analogous to that of idiopathic acquired haemolytic anaemia, and that the splenic functions concerned are those of sequestration and destruction of thrombocytes rendered susceptible by antibody sensitization, together with a possible initial contribu-

tion to the formation of the antibodies. Further studies reported by Stefanini (1955) throw some light on these possibilities. First, splenectomy does not apparently influence the titre and activity of platelet antibodies, although administration of corticotrophin or cortisone does significantly decrease the antibody level. Second, the thrombocytopenic effect of injected I.T.P. plasma in experimental animals was greatly reduced by previous splenectomy or ligation of the splenic artery in the recipient. These results perhaps suggest that the contribution of the spleen to antibody formation in this disease is not of great importance, and that its thrombocytolytic role is paramount, but observations on this point have so far been few, and it is too early to draw any firm conclusions.

Hypersplenism. Hypersplenism is a state in which an enlarged and over-active spleen is primarily responsible for the development of neutropenia, anaemia, or thrombocytopenia, or a combination of these cytopenias. The bone-marrow shows normal or increased cellularity, although there may be evidence of maturation arrest of one or more cell-series. It should be made clear at this stage that we do not regard the conditions, already discussed, of hereditary spherocytosis and acquired auto-immune haemolytic anaemia as examples of hypersplenism, although they have been so regarded by many haematologists in the past (Doan, 1949; Sturgis, 1953). In this matter we are in accord with the views of Dameshek (1955), since it appears indisputable that the fundamental abnormality directly responsible for the cytopenia in both these disorders lies chiefly outside the spleen, and that the splenic contribution, though often essential to the full development of the clinical syndrome, is mainly secondary. It will be clear from the earlier discussion that the position of idiopathic thrombocytopenic purpura is less certain. An element of hypersplenism may be of primary importance in, at least, some cases of chronic I.T.P., in which an immunological mechanism is not evident, and may coexist with such disorder in others.

Hypersplenism has been described in many conditions involving splenomegaly. The splenic enlargement may be apparently primary, without specific pathological changes in the organ, but more commonly it is due to some recognizable cause, as in Banti's syndrome of congestive splenomegaly in portal hypertension, or in the reticulo-endothelial disorders ranging from lymphosarcoma, reticulum-cell sarcoma, and the varieties of lymphadenoma to the lipid-storage diseases. There may be evidence of hypersplenism in leukaemias with splenomegaly and in myelofibrosis, and indeed almost any disorder with gross splenic enlargement may be complicated by hypersplenic cytopenias (Scott, 1949; Sturgis, 1953; Dameshek, 1955). The process by which the enlarged spleen in these disorders produces the haematological manifestations is a subject of dispute. At least three splenic functions have been thought to be involved by reason of their over-activity. These are sequestration and phagocytosis, the production of a marrow-regulating hormone, and the formation of auto-antibodies. The first of these functions has been particularly emphasized by Wiseman and Doan (1939), Doan and Wright (1946), Doan (1949), and Wright,

Doan, Bouroncle, and Zollinger (1951). They claimed that an excessive post-adrenaline increase of the affected cells in the blood is to be found in splenic cytopenias, due to release from sequestration when splenic contraction occurs, that such sequestration and phagocytosis can be demonstrated in supravital studies of tissue obtained at splenectomy, and that splenic venous blood shows a lower concentration of affected cells than does splenic arterial blood, indicating a selective trapping effect. Each of these observations has been disputed by Dameshek and his group (Chatterjea, Dameshek, and Stefanini, 1953; Stefanini, Chatterjea, Dameshek, Welch, and Swenson, 1952). Studies in our own laboratories have led us to question the value of the adrenaline test in hypersplenism (Robertson-Smith and Hayhoe, 1951), but we have found differences between counts of splenic arterial and venous blood which lend some support to the views of Doan (Bell and Alton, 1955). The hypothesis of excessive hormone production by the spleen, strongly advocated by Dameshek in many publications since 1947, has been supported chiefly by the finding of maturation arrest in the bone-marrow before splenectomy, with a return to normal after operation. Although this arrest of development may involve granulocytes, it is most conspicuous in cases of idiopathic thrombocytopenic purpura, and we cannot in the present state of our knowledge regard the latter condition as unequivocally hypersplenic in origin. Moreover, the absence of any certain proof of the existence of a splenic hormone is a major difficulty in the way of accepting this attractive hypothesis.

Finally, the occurrence of a positive erythrocyte antiglobulin test, or other evidence of auto-antibody formation, in some cases of secondary hypersplenism has suggested that this aspect of splenic function may also be involved. It is over this question that a radical revision of our approach to the whole concept of hypersplenism is becoming necessary. Hypersplenism is a diagnosis arrived at by exclusion; if no potential cytopenogenic mechanism can be demonstrated outside the spleen, and the spleen is enlarged, hypersplenism, either primary or secondary, has been tentatively diagnosed in recent years when peripheral cytopenias and an active marrow are found. Improvement after splenectomy has been taken to justify the diagnosis. It is obvious, however, from consideration of such conditions as hereditary spherocytosis, that amelioration after splenectomy in no way indicates a primary role of the spleen in a given disorder. Successful splenectomy in supposed hypersplenism does not in fact justify the diagnosis or throw much light on the essential pathogenetic mechanism. The spleen might be overactive, but some extrasplenic factor might equally well be responsible, by acting on cells in such a way as to prevent their maturation in the marrow and to render them susceptible to destruction by normal splenic activity in the peripheral blood. Such a factor is now known to exist in primary acquired auto-immune haemolytic anaemia and in many cases of idiopathic thrombocytopenic purpura, conditions thought earlier to be unequivocally hypersplenic. Evidence is gradually accumulating that a similar immuno-allergic basis may account for many cases of isolated or combined cytopenias, both primary and secondary to an established disease. In haemolytic anaemias

associated with splenomegalic leukaemias and reticulo-endothelial hyperplasias auto-immunization is frequently demonstrable (Jordan and Dingle, 1949; Rosenfield, Vogel, and Rosenthal, 1951; Willcox, 1952; Sulzer, 1952; Paraf and Dausset, 1952; Hennemann, Kunz, and Gillert, 1953; Dacie, 1954*c*), and may perhaps exist more commonly than it is detected by present techniques. Leucocyte agglutinins have recently been demonstrated in many cases in which leucopenia would otherwise have been ascribed to primary or secondary hypersplenism. Thus Moeschlin (1955) has reported their occurrence in the neutropenias of Felty's syndrome, splenic tuberculosis, lupus erythematosus, plasmacytoma, and infectious mononucleosis, while Dausset and Nenna (1952, 1953) have shown their presence in leucopenias of apparently primary nature. Similar observations have been made by Kissmeyer-Nielsen (1953), Miescher (1953), and others. Auto-agglutinins for platelets have also been detected in some cases of secondary thrombocytopenia in patients with leukaemia and lupus erythematosus (Harrington, 1954), although the majority of such patients do not have readily demonstrable antibodies.

In all such cytopenias, and perhaps in many others in which refinements of serological technique may eventually disclose humoral abnormalities, the label of hypersplenism ought now to be used with considerable reserve. Certainly the splenic component in total pathogenesis may be large, and the spleen may contribute to antibody formation and may selectively remove damaged cells, but the primary mechanism would appear to involve the widely disseminated lymphoreticular antibody-producing system.

Whatever the pathogenesis of these primary and secondary 'hypersplenic' states, and whatever our reservations as to the validity of this diagnosis, there is no doubt that splenectomy may greatly benefit some patients with cytopenias who have an active bone-marrow and splenomegaly, especially when the disease is primary, or, if secondary, when the underlying disorder is chronic and the haematological features severe (Scott, 1949). Brief details of 11 such patients are given in Table II, from which it will be seen that splenectomy achieved some degree of success in every case. Fuller case reports of three of these patients are given below. For comparison, further brief records of six patients with peripheral cytopenias, but without appreciable splenomegaly, and with marrow hypoplasia, are provided in Table III. These patients, in all of whom any question of a toxic or noxious marrow aplasia was so far as possible excluded, were all examples of primary hypoplastic pancytopenia (primary aplastic anaemia), and were treated by splenectomy on the grounds that the operation was unlikely to do harm and might perhaps produce some improvement, particularly in the platelet count. Splenectomy was uniformly unsuccessful. A more complete case report of one of these patients, in whom the diagnosis of hypersplenism was initially entertained, is also given below.

10. *C. C., a man aged 50 years. Primary hypersplenic pancytopenia.* This patient was first admitted to hospital in April 1953, with a history of increasing lassitude, dyspnoea, cough, and loss of weight during the previous four months. He was pale, and looked ill. Physical examination revealed an enlarged spleen

extending to the umbilicus, and slight bilateral oedema of the ankles, but no other significant physical signs. Investigations showed a gross leucopenia, with total leucocytes varying between 600 and 1,300 per c.mm. The leucopenia involved all cell-types, but particularly neutrophils. A diminution in platelets to 50,000 per c.mm. was also present, and the haemoglobin level was 10 gm. per 100 ml. Numerous investigations were carried out during the next month, the essential relevant findings being a persistent anaemia and leucopenia, with a less constant thrombocytopenia. Reticulocytosis of the order of 5 to 10 per cent., together with increased serum-bilirubin (from 0·5 to 2 mg. per cent.) and

TABLE II

Effects of Splenectomy in Cases of Primary or Secondary Cytopenia with Splenomegaly and Marrow Hyperplasia

Patient, age (years), and sex	*Diagnosis*	*Extent of splenomegaly*	*Status before operation*	*Status after operation*	*Extent of response to splenectomy*
F. P., 43, M	Primary pancytopenia with active marrow	+	Severe non-haemolytic anaemia, with negative Coombs test. Gross neutropenia (200 per c.mm.) and thrombocytopenia (40,000 per c.mm.). Marrow actively cellular, with conspicuous granulocyte maturation arrest. Required frequent transfusion	Improvement in anaemia. Transfusion requirements substantially decreased. Otherwise unchanged	Partial
E. F., 49, F	Primary 'hypersplenic' neutropenia and anaemia	++	Moderate anaemia (haemoglobin 7–9 gm. per 100 ml.), with positive antiglobulin test; serum-bilirubin 1·6 mg. %; reticulocytes 2–7%; normal fragility. Severe leucopenia (1,700 per c.mm., with 300 neutrophils per c.mm.). Platelets normal	Good immediate response; haemoglobin maintained at 12–13 gm. per 100 ml. for last 5 years. Coombs test unaltered. Leucocytes maintained at 8–12,000 per c.mm., with neutrophils varying from 200 to 1,500 per c.mm.	Good
B. J., 33, F	Primary 'hypersplenic' anaemia	+	Severe macrocytic anaemia, with no definite evidence of haemolysis and negative antiglobulin test. Leucocytes and platelets normal. Marrow hyperplastic, with myelo-erythrogenetic ratio 1:1, but no maturation arrest. Required frequent blood transfusions, and did not respond to haematinics	Immediate response well maintained for a 3-year follow-up period, with a normal blood picture apart from persistent macrocytosis	Complete
D. W., 12, M	Primary 'hypersplenic' pancytopenia, with predominating neutropenia	++	Mild non-haemolytic anaemia (haemoglobin 8–10 gm. per 100 ml.), with marked thrombocytopenia (20,000–100,000 per c.mm.) and very severe neutropenia (100–400 per c.mm.). Frequent minor infections. Active sternal marrow, with granulocyte maturation arrest	Platelets and erythrocytes returned rapidly to normal, and this improvement has been maintained for several years. Neutrophils returned initially to normal, but relapsed after 3 months, and have since persisted at 400–1,500 per c.mm.	Partial
C. C., 50, *M	Primary 'hypersplenic' pancytopenia	+++	Moderately severe haemolytic anaemia, with normal erythrocyte osmotic fragility and negative antiglobulin tests; marked leucopenia (600–1,300 per c.mm.) and thrombocytopenia (50,000 per c.mm.). Active marrow, with normoblastic preponderance and granulocyte maturation arrest	Rapid return to normal both clinically and haematologically. Haemoglobin 13–14 gm. per 100 ml. Leucocytes 4,000 per c.mm. Platelets 360,000 per c.mm.	Complete
D. M., 59, F	Pancytopenia secondary to lymphosarcoma	+++	Moderately severe haemolytic anaemia, with slightly increased erythrocyte osmotic fragility and negative antiglobulin tests. Variable neutropenia. Variable thrombocytopenia (60,000–150,000 per c.mm.). Bone-marrow hyperplastic. Lymphosarcoma involving lymph-nodes, spleen, and liver	Marked improvement in anaemia and thrombocytopenia, with substantially normal figures. Leucocyte increase, but persistent tendency to some neutropenia. Condition has remained good in 2-year follow-up (radiotherapy given for primary condition)	Good

* Fuller case report given in text.

Patient, age (years), and sex	Diagnosis	Extent of splenomegaly	Status before operation	Status after operation	Extent of response to splenectomy
A. H., 46, *M	Anaemia and thrombocytopenia secondary to subacute lymphatic leukaemia	+++	Severe anaemia, with no clear evidence of haemolysis. Normal erythrocyte fragility; a cold auto-agglutinin of high thermal amplitude present. Weakly positive antiglobulin test. Platelets 20,000–150,000 per c.mm. Required very frequent transfusions. Leukaemia chiefly aleukaemic, with occasional leucocyte increase to 30,000 per c.mm. Neutrophils variable (2,000–5,000 per c.mm.). Only temporary improvement with cortisone	Substantial improvement in anaemia (haemoglobin stabilized around 8–10 gm. per 100 ml.). Transfusions no longer required. Platelets 150,000–300,000 per c.mm. Leukaemia controlled with triethylene melamine	Good
R. B., 50, M	Pancytopenia secondary to Hodgkin's disease	+++	Severe anaemia, non-haemolytic; normal erythrocyte fragility; negative antiglobulin tests. Required frequent transfusions. Variable leucopenia and thrombocytopenia. Response to triethylene melamine good but temporary. Marrow actively cellular, normoblasts predominating	Good immediate response in all blood elements, which became steady at near normal figures, but relapse occurred after 2 months with rapid uncontrollable deterioration	Good (temporary)
E. A., 45, *F	Pancytopenia secondary to congestive splenomegaly	+++	Moderately severe anaemia, with normal erythrocyte fragility and negative antiglobulin tests, but some evidence of haemolysis. Leucopenia (1,650 per c.mm.) and thrombocytopenia (50,000 per c.mm.). Marrow normal. Portal hypertension due to extrahepatic venous obstruction	Full clinical and haematological recovery, with return of blood counts to normal	Complete
P. T., 17, M	Thrombocytopenia and marginal neutropenia secondary to congestive splenomegaly	++	Hepatic cirrhosis, with moderate portal hypertension and splenomegaly. Occasional anaemia from gastrointestinal haemorrhages, but otherwise not anaemic. Neutropenia (1,000–2,000 per c.mm.). Marked thrombocytopenia (30,000–60,000 per c.mm.). Active marrow, with evidence of megakaryocyte maturation defect	No further haemorrhages since operation 4 months ago. Neutropenic tendency persists. Platelets rose to 360,000 per c.mm., but have since fallen to 150,000 per c.mm.	Partial
W. B., 49, M	Pancytopenia in disseminated tuberculosis	+	Pancytopenia with non-haemolytic anaemia, requiring repeated transfusion, neutropenia (500–1,500 per c.mm.), and thrombocytopenia (60,000–100,000 per c.mm.). Actively cellular marrow. No diagnostic physical signs of tuberculosis, and investigations negative prior to operation	No change apart from neutrophil increase to 6,000–10,000 per c.mm. Platelet level and progress of anaemia not significantly affected	Slight

TABLE III

Effects of Splenectomy in Cases of Primary Hypoplastic Pancytopenia

Patient, age (years), and sex	Diagnosis	Extent of splenomegaly	Status before operation	Status after operation	Extent of response to splenectomy
C. H., 68, M	Primary hypoplastic pancytopenia	–	Severe anaemia of aplastic type; frequent transfusions required. Leucocytes 500–1,500 per c.mm. Platelets 25,000–100,000 per c.mm. Marrow hypoplastic, with evidence of granulocyte maturation arrest	Unchanged, apart from slight increase in leucocytes to 1,000–3,000 per c.mm. No decrease in transfusion requirements	None
B. G., 64, M	Primary hypoplastic pancytopenia	–	Gross anaemia, with severe leucopenia (500–1,000 per c.mm.) and thrombocytopenia (10,000–50,000 per c.mm.). Hypoplastic marrow. Episodes of bleeding from gut. Frequent transfusions required	Unchanged	None
A. B., 44, F	Primary hypoplastic pancytopenia	–	Severe anaemia; frequent transfusions needed. Gross leucopenia (200–1,000 per c.mm.) and thrombocytopenia (10,000–30,000 per c.mm.). Marrow very hypoplastic	Unchanged, apart from some improvement in thrombocytopenia	None

* Fuller case report given in text.

TABLE III (*cont.*)

Patient, age (years), and sex	*Diagnosis*	*Extent of splenomegaly*	*Status before operation*	*Status after operation*	*Extent of response to splenectomy*
A. F., 25, F	Primary hypoplastic pancytopenia	–	Mild fluctuating anaemia, unresponsive to haematinics. Saline fragility of red cells normal; Coombs test negative. Persistent marked neutropenia and thrombocytopenia. Marrow hypoplastic	Unchanged	None
A. K., 19, M	Primary hypoplastic pancytopenia	–	Severe anaemia. No evidence of haemolysis. Neutropenia (200–1,000 per c.mm.). Thrombocytopenia (40,000–90,000 per c.mm.). Hypoplastic marrow. No response to haematinics. Frequent transfusion needed	Unchanged	None
J. H., 22, *M	Primary hypoplastic pancytopenia (with initially active marrow)	±	Severe anaemia, with no evidence of haemolysis; marked neutropenia (650 per c.mm.) and thrombocytopenia (20,000 per c.mm.). Marrow initially cellular and active, with some granulocyte-maturation arrest	Unchanged The marrow *post mortem* was hypoplastic	None

* Fuller case report given in text.

excess of urinary and faecal urobilinogen, suggested haemolysis. Direct and indirect antiglobulin tests were repeatedly negative, and the saline osmotic fragility of the erythrocytes was normal. Hepatic function tests gave normal results, although a barium swallow suggested slight oesophageal varices. Chest X-rays were clear. Sternal-marrow aspirates showed active hyperplasia, with marked erythropoietic predominance and some evidence of granulocyte maturation arrest. Splenectomy was performed on July 1; at operation the liver was normal in appearance, and portal venous pressure and a portal venogram were also normal. A rapid spontaneous improvement in the clinical and haematological condition ensued after operation, and two months later the haemoglobin concentration was 13·7 gm. per 100 ml., the leucocyte count 4,000 per c.mm., and the platelets 360,000 per c.mm. The patient was clinically very well at the time of discharge from hospital, but has not returned for further follow-up examination.

11. *A. H., a man aged 46 years. Anaemia and thrombocytopenia secondary to subacute lymphatic leukaemia.* This patient first became ill in 1951, when there was an insidious onset of lassitude, with gradually increasing weakness, exertional dyspnoea, and pallor. When admitted to hospital in September 1952 he was very pale, with generalized lymph-node enlargement, the liver was palpable, and the spleen extended to below the umbilicus. Haemoglobin was 3·8 gm. per 100 ml., leucocytes 8,800 per c.mm. (lymphocytes 58 per cent.), and platelets 150,000 per c.mm. The sternal marrow showed marked lymphocytic infiltration, with erythroid hypoplasia. A lymph-gland biopsy showed the appearances of lymphatic leukaemia. In spite of frequent transfusions the haemoglobin could not be maintained at a reasonable level. Transfused blood was lost very rapidly, although there was no clear evidence of haemolysis, and the serum-bilirubin and faecal urobilinogen levels did not rise. Cortisone in doses of 100 to 250 mg. per day was successful in substantially decreasing the patient's transfusion requirements, and for 15 months he was maintained in a precarious condition, with several admissions to hospital for transfusion. There was then a severe relapse, uncontrolled by cortisone, and the leucocyte count rose to 30,000 per c.mm., with occasional blast cells in the peripheral blood. The gross anaemia remained the critical problem at this stage. There was still no clear evidence of haemolysis, but there was a weakly positive antiglobulin test, together with a high serum-globulin level (6 gm. per 100 ml.) and a strong cold auto-agglutinin of

high thermal amplitude. Although the massive size of the spleen and the presence of several adhesions made the operation a formidable one, splenectomy was successfully performed in March 1954, in the hope that red-cell survival would be increased and that the platelet level, which was between 20,000 and 60,000 at this time, might rise. Massive transfusion of 16 pints of packed cells succeeded in raising the haemoglobin level to 8·5 gm. per 100 ml. before operation, but immediately after operation it fell sharply to 6·5 gm. per 100 ml. A steady increase, with some reticulocytosis, then ensued, and the haemoglobin concentration has remained between 8 and 10 gm. per 100 ml. for the last 14 months. The platelet count has varied between 150,000 and 300,000 per c.mm. during this period, and the leukaemic manifestations of lymph-node enlargement and leucocytosis have been well controlled by short courses of triethylene melamine. Transfusions have not been required, and the patient has been able to return to part-time work.

12. *E. A., a woman aged 45 years. Congestive splenomegaly with pancytopenia.* This patient in January 1952 complained of pallor for the last year or two, shortness of breath for two or three months, and lassitude for two months. There was anorexia and occasional nausea, but no epigastric pain or vomiting, and no history of constipation, diarrhoea, or melaena. She was pale, with a sallow complexion and a slightly icteric tinge. There was no palmar erythema, no spider naevi, and no palpable glands, and the tongue was normal. A large, firm spleen extended to well below the umbilicus. There was no detectable ascites, and no external evidence of venous collaterals in the abdominal wall. No other significant physical signs were encountered. A blood count showed haemoglobin 8 gm. per 100 ml., with mean corpuscular volume 90 c.μ and mean corpuscular haemoglobin concentration 32·8 per cent., and leucocytes 1,650 per c.mm., with a marked depression of both neutrophils and lymphocytes. Platelets numbered 50,000 per c.mm. Reticulocytes were 3·6 per cent., and the serum-bilirubin was 0·9 mg. per 100 ml. There was no spherocytosis, erythrocyte saline fragility was normal, and antiglobulin tests were negative. The marrow was normally cellular. Several examinations for occult blood in the faeces were negative, and barium-swallow examinations failed to reveal oesophageal varices. Numerous biochemical tests of hepatic function gave variable results, with no unequivocal evidence of abnormality. At laparotomy (Mr. A. Hunt) the liver was found to be normal, with no sign of cirrhosis, but the left kidney was lying behind the root of the mesentery to the right of the mid-line, compressing the superior mesenteric vein, and the portal venous pressure was 400 mm. citrate. A portal venogram showed an otherwise normal portal tract. The left kidney was replaced in the normal position, and the enlarged and congested spleen mobilized and removed. After operation there was a gradual but complete return to normal in both clinical and haematological aspects; six months later the haemoglobin was 13 gm. per 100 ml., leucocytes 10,000 per c.mm., with a normal differential count, and platelets 500,000 per c.mm. Subsequent progress has been excellent apart from the development of a mild iron-deficiency anaemia two years later, which responded to appropriate treatment. The histological appearance of the spleen was that of congestive splenomegaly.

13. *J. H., a man aged 22 years. Pancytopenia with active marrow and slight splenic enlargement.* This patient came under our care in January 1952, with a history of rapidly increasing weakness, lassitude, and headaches during the previous two months. He was very pale, the spleen was just palpable, and there were small bilateral retinal haemorrhages and a moderately positive capillary-resistance test, but no other positive physical signs. Blood examination showed

haemoglobin 5·2 gm. per 100 ml., with mean corpuscular volume 113 c.μ and mean corpuscular haemoglobin concentration 37 per cent., reticulocytes 0·9 per cent., and considerable macrocytosis, anisocytosis, and poikilocytosis of the red cells in stained films. Leucocytes numbered 2,000 per c.mm., with 650 neutrophils and 1,300 lymphocytes per c.mm. Platelets totalled 20,000 per c.mm., and the bleeding time was greatly prolonged. Sternal-marrow examination showed a very cellular, highly active marrow, with normal differential cytology except for some suggestion of maturation arrest in the granulocyte series. Erythrocyte saline fragility was normal, and the antiglobulin test was negative. This general picture was suggestive of splenic pancytopenia, although the splenomegaly was questionably slight. Splenectomy was performed in February, but led to no improvement either clinically or haematologically. The patient's subsequent course was steadily downhill in spite of frequent transfusions and adequate haematinics, and death occurred three months later from cerebral haemorrhage and severe pancytopenia. The marrow *post mortem* appeared generally hypoplastic, and sections confirmed this impression. In retrospect the diagnosis must have been primary 'aplastic' anaemia, with areas of temporary hyperplasia in the marrow. Section of the spleen did not show any significant pathological change, and in particular there was no evidence of phagocytic over-activity.

Our experience of splenectomy in primary and secondary 'hypersplenism' has therefore been favourable when the criteria of maintained marrow activity and substantial splenomegaly have been present. The failure of the operation in all our cases of hypoplastic anaemia has led us to abandon this approach in typically 'aplastic' patients, but we should feel the small operative risk justified if either moderate marrow cellularity or palpable splenomegaly were found. The value of splenectomy in secondary 'hypersplenism' arising during the course of leukaemia and myelosclerosis is not easy to assess. Both diseases have commonly been regarded as contra-indications to operation, the first because plausible extrasplenic causes for anaemia and thrombocytopenia exist and leukaemic patients incur greater risk at operation, the second because the spleen in myelosclerosis has been thought to subserve a vital haemopoietic function, through myeloid metaplasia, when the marrow is largely fibrotic. Nevertheless, when transfusion requirements in such patients become very heavy, and latent or overt haemolysis gravely threatens life, splenectomy has sometimes been followed by remarkably successful diminution in this aspect of the disease. Case report no. 11 illustrates such a response in leukaemia, while similar successes have been recorded in myelosclerosis (Loeb, Moore, and Dubach, 1953).

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Summary

1. Among the physiological activities of the spleen are included reservoir function and sequestration of erythrocytes, haemopoietic activity at certain

phases of life, phagocytic and reticulo-endothelial activity, possibly hormone production, and capacity to elaborate antibodies. The evidence for the existence and importance of each of these functions is surveyed.

2. Although splenectomy is uniformly successful in hereditary spherocytosis, there is no primary disorder of splenic function. The disease is thought to be due to a fundamental inherited defect in erythrocyte architecture and enzymatic constitution, which leads to deformity and spherocytosis. The spherocytes are selectively destroyed by the exercise of a normal splenic activity.

3. In auto-immune idiopathic acquired haemolytic anaemia the spleen contributes partially to the formation of auto-antibodies, and phagocytic reticulo-endothelial activity may be increased, but the disease may best be regarded as a primary disorder of the plasma-protein- and antibody-forming mechanism.

4. Idiopathic thrombocytopenic purpura, previously believed to be a disease due primarily to splenic hormonal or phagocytic over-activity, must now be regarded, at least in a substantial proportion of cases, as immuno-allergic in origin. The splenic contribution to auto-antibody formation in this disease may not be of great importance, and the success of splenectomy in many cases may be attributable chiefly to the removal of a major thrombocytolytic site.

5. Many of the combined or isolated cytopenias associated with active bone-marrow and splenomegaly, usually regarded as examples of primary or secondary hypersplenism, may in fact be further immuno-allergic disorders, with a primary abnormality involving the antibody-producing system. Nevertheless splenectomy is often successful in such cases, whether by removal of a site of antibody-formation, by reduction in cytolysis, or by removal of an organ producing an excess of marrow-regulating hormone.

6. Primary hypoplastic pancytopenias without splenomegaly do not improve after splenectomy, but operation might be justified if palpable splenomegaly or a moderately active marrow were encountered in an otherwise typical aplastic anaemia.

7. In leukaemia and myelosclerosis, when transfusion requirements are large, splenectomy may produce great improvement in the anaemic state, especially if evidence of haemolysis is found.

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THE PAIN OF PEPTIC ULCERATION[1]

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THE origin of the characteristic pain of uncomplicated peptic ulceration of the stomach and duodenum has for many years been the subject of speculation and discussion, and three main theories have emerged. The first, the 'acid theory', ascribes the pain to irritation of the ulcer base by the acid of the gastric juice, and the second, the 'motility theory', relates the pain to the muscular activity, normal or abnormal, of the stomach or duodenum. According to the third view the inflammatory reaction around the ulcer is itself the cause of the pain, *dolor* being associated in the usual way with *calor*, *rubor*, and *tumor*.

Acid Theory

The acid theory has an obvious appeal. Hydrochloric acid is an irritant substance which, when applied to the skin, produces erythema and a burning sensation, and it appears reasonable to suppose that the hydrochloric acid of the gastric juice, if present in sufficient concentration, would irritate the raw ulcer base and cause pain. There is ample clinical evidence that acid does play some part in the production of ulcer pain, since relief is obtained if the acid gastric contents are either neutralized by the administration of alkalis or removed by vomiting or aspiration.

Many workers have sought to confirm the acid theory experimentally by showing that pain occurs when hydrochloric acid is introduced into the stomach through a gastric tube. One of the first to use this method successfully was Talma (1884), who introduced 500 ml. of 1:75 solution of hydrochloric acid into the stomachs of two patients, one of whom was probably suffering from peptic ulceration. The other patient had cancer of the stomach. Later workers, including Bönniger (1908) and Heineke and van Selms (1908), have confirmed this work in cases of peptic ulceration, although it must be pointed out that the concentration of the hydrochloric acid was generally greater than that found in the gastric juice. The chief exponents of this method, and of the acid theory of pain, have been Palmer in the United States of America, and Pickering in Britain. Palmer (1926*b*) reported the results of 443 experiments which he had performed on 109 patients who suffered from peptic ulceration. His technique was to introduce 200 ml. of 0·5 per cent. hydrochloric acid into the stomach, and to repeat the dose after half an hour if the first injection failed to produce pain. The injection of acid caused pain in 324 experiments, but failed to do so in the other 119, 105 of which were conducted during so-called distress-free periods—

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that is to say, the patient had had no spontaneous ulcer symptoms during the preceding 24 hours. Fourteen of the 119 'failures' occurred during a period when the patients were suffering from frequent spontaneous attacks of pain. Palmer admitted that 0·5 per cent. hydrochloric acid was about twice the physiological concentration of acid in the gastric juice, but he said that he had been able to produce pain with concentrations of 0·1 per cent. and 0·2 per cent. hydrochloric acid. He attributed the pain to the injection of acid even when the interval between the injection and the onset of the pain was as long as an hour or more, and he occasionally found that it continued for 40 minutes after neutralization of the gastric contents. Distress could also be produced with 0·4 per cent. sulphuric acid, 3 per cent. acetic acid, and N/10 sodium hydroxide, and, perhaps more important, in some experiments it resulted when he reintroduced acid stomach contents, the aspiration of which had previously afforded relief. Thirty subjects, whose stomachs were normal, suffered no real pain during experiments with acid injection, although one had a slight burning sensation. Seven were nauseated, and four vomited. Reviewing the position in 1934, Palmer and Heinz concluded that ulcer pain arose at the site of the lesion, and that the usual stimulus was the free hydrochloric acid of the gastric juice, although it was possible that at times an adequate stimulus could be provided by peristaltic contraction or local spasm.

Bonney and Pickering (1946–8) confirmed Palmer's results. They found that 200 to 300 ml. of N/20 to N/10 hydrochloric acid produced pain about 10 minutes after its introduction into the stomach. The discomfort could then be abolished by emptying the stomach, or by neutralizing the gastric contents with alkali. The delay between neutralization and relief of symptoms was about eight minutes. When the stomach contents were sampled at half-hourly intervals during spontaneous attacks of pain, it was found that symptoms began when the stomach contents became more acid, and ceased when the acidity decreased. Pain never occurred in a given patient when the gastric acidity was less than a certain value for a given time. Some agreement was found between the levels of acidity which were associated with pain after the injection of acid and those which obtained during spontaneous attacks. The authors thought that the latent period between the introduction of acid and the onset of discomfort represented the time taken by the acid to penetrate through the necrotic material in the ulcer crater before reaching the sensitive nerve-endings in the ulcer base.

Against this formidable array of evidence there is the failure by many reliable workers to produce pain by injecting acid into the stomach. Included in this number were Schmidt (1908), Hurst (1910), Boring (1915), Ginsburg, Tumpowsky, and Hamburger (1916), and Carlson (1918). These authors used concentrations of hydrochloric acid ranging from 0·5 per cent. to 5 per cent. Hurst, who was convinced that acid was not the direct cause of the pain of peptic ulcer, introduced four ounces of 0·5 per cent. hydrochloric acid in his experiments in six cases of gastric ulcer, without causing symptoms. Nevertheless, it should be noted that Palmer used two to four times this amount of acid. In the hands of

Ginsburg and his colleagues 70 ml. of 5 per cent. hydrochloric acid produced a burning feeling and vomiting, but no typical pain. Boring failed to produce more than a feeling of hunger with 5 per cent. hydrochloric acid. Wolf and Wolff (1947*b*), in their remarkable series of observations on 'Tom', found that strong acid applied to the inflamed and even eroded gastric mucosa, through the fistula, did not cause pain, and they could obviously be certain that the acid was brought into direct contact with the eroded area. On the other hand, pinching such an area did result in pain.

If there is a discrepancy of opinion about the ability of acid to produce pain experimentally, there is equal disagreement about its occurrence in the absence of free acid. Palmer (1926*a*) and Pickering (1952) dismissed reports of pain associated with achlorhydria as being unreliable or misleading, believing that free acid would have been demonstrated at some time if more frequent samples of gastric juice had been obtained, if the end of the tube had been at the right level in the stomach, or if histamine had been given. Nevertheless, Ryle (1925) and Kinsella (1928) have reported patients with gastric and duodenal ulceration who have had pain which could be relieved by food and alkali, but who have had achlorhydria, and Hardt (1918, 1922) reported pain when there was no free acid in the gastric juice. Further, it is well known that many people who have the typical pain of peptic ulceration are found to have no ulcer demonstrable by X-ray examination, or even by direct examination at operation. There is thus some evidence that an 'ulcer type' of pain can occur in the absence of free acid, and even in the absence of an ulcer. As Alvarez remarked (1939), 'When one examines a man with hunger pain relieved by alkalies and finds an achlorhydria which persists during the eating of several Ewald meals, one should not throw out this record as meaningless and to be forgotten simply because with the help of histamine one can secure a few drops of acid. Knowledge is not obtained by rejecting embarrassing data.' Acid must surely be a factor in the production of ulcer pain, but there is evidence to suggest that it is not the only factor, and may not even be the essential one. There is, for instance, the difficulty of explaining the rapid relief of symptoms on going to bed, when the hyperchlorhydria is unaltered and the ulcer unhealed.

Motility Theory

Supporters of the motility theory usually attribute the pain of peptic ulceration to the peristaltic contractions of the stomach or duodenum, or to local spasm. The peristaltic contractions may be painful in themselves, or they may, like the local spasm, cause pain by compressing the ulcer. Ewald (1891–2) noticed that the surface of an ulcer was distorted, and the nerves irritated, by the contractions accompanying digestion. In 1911 Hurst propounded the view that tension was the only true cause of visceral pain. He thought that strong gastric peristaltic waves would cut off the prepyloric region from the rest of the stomach, and that the pressure in this segment would then rise until it was sufficient to force the chyme into the duodenum. If the pylorus failed to relax

the pressure would rise still farther, and the tension in the prepyloric muscle-fibres would increase to the point of causing pain. Hurst believed that acid stimulated gastric peristalsis and inhibited relaxation of the pylorus. This effect would be greater in the presence of an ulcer, since the reflexes were more easily stimulated through bared nerve-endings in the ulcer base. The experimental basis for the motility theory was put forward by Cannon and Washburn (1911–12) who, by means of the balloon-kymograph technique, claimed to demonstrate that hunger pains in normal people coincided with vigorous gastric contractions. Ginsburg, Tumpowsky, and Hamburger (1916), investigating 10 patients with peptic ulcer, and using a similar balloon-kymograph method, found that spasms of pain were associated with peristaltic contractions. Carlson (1918) repeated these studies on a student who had a peptic ulcer, and pointed out that the contractions which were associated with pain were no more vigorous than the hunger contractions which occurred in a normal individual. He thought that the pain must be due to increased sensitivity of the nerve-endings. Hardt (1918, 1922), by inducing his patients to swallow two tubes, one of which carried a balloon, was able to study both the motility of the stomach and the acidity of its contents. He demonstrated the concurrence of pain and contractions in the absence of free acid. In 1928 Wilson, as the result of X-ray studies, found in 13 of 16 cases of duodenal ulcer that filling of the duodenal cap with barium by pressure on the anterior abdominal wall was followed by relief of pain. In 10 of these 13 cases there was a high concentration of free acid in the gastric contents at the time of the experiment. The relief of symptoms was extremely short-lived, and lasted in some cases for only a few minutes. Wilson thought that pain was due to overaction and contraction of the caput of the duodenum, and relief of pain to its relaxation.

Patterson and Sandweiss (1942) reported some interesting observations on four patients who had duodenal ulcers. They made 21 simultaneous recordings of gastric and duodenal motility, and showed that ulcer distress occurred only when the duodenum was active. The stomach might or might not be active at the same time. If the patients experienced severe ulcer pain for 15 to 18 minutes or more, the duodenal motility pattern became abnormal and tone increased until a state resembling that of incomplete tetanus was reached. Having made these observations, which supported the motility theory, they then discovered that alkali introduced into the stomach through a tube relieved the distress but did not alter the motility record. Ortmayer (1925) was convinced that ulcer pain and peristaltic contractions were unrelated; and Palmer was sure that motor activity played a very small part in the production of ulcer symptoms. In 1927, when he investigated the role of peristalsis and spasm, Palmer used the balloon-kymograph technique, and also screened his patients after giving them barium made up in a solution of 0·5 per cent. hydrochloric acid. During his balloon-kymograph studies he observed the occurrence of pain synchronous with contractions only 19 times, as opposed to 198 occasions on which pain occurred in the absence of contractions. During screening he failed to notice any disturbances of motility which could be related to the occurrence of pain.

Inflammatory Theory

Kinsella (1929, 1948) has for many years championed the theory that ulcer pain is caused directly by the inflammatory reaction associated with the ulcer. Ivy (1939) also believed that the continuous pain of ulceration was due to the congestion and oedema which were part of the inflammation. In 1953 Kinsella strengthened his case by examining microscopically the sections taken from 22 gastric ulcers. He searched for nerves in the four Askanazy layers of inflammatory tissue in the ulcer base, and found that degeneration began in the fibrous layer and was complete in the granulation layer. The more superficial leucofibrinous and eosinophil-necrotic layers contained only a few ghostly remains of nerves, and moreover these two layers were shown to be impermeable to the acid of the gastric juice. Kinsella based this latter statement on the observation that leucocytes in the leucofibrinous layer showed no signs of digestion by the gastric juice, nor did some meat-fibres which happened to be embedded in the layers of one of the ulcers. The sides of the ulcers contained numerous healthy nerves, but these were generally drawn away from the ulcer edge by the retracting muscular coat under cover of the intact but thickened submucosa. The nerves of the edge were inaccessible to gastric acid. He found it difficult to believe that acid could cause pain by irritating nerve endings in the ulcer if the nerve endings were quite inaccessible. On the other hand, pain could be caused by the direct action of inflammation on the nerves in the edge of the ulcer. Kinsella went on to attempt to explain the relief of pain, after food, alkali, or vomiting, on a complex haemodynamic basis. He suggested that the periodicity of ulcer pain, and its relief by food and alkali, might be related to changes in the degree of congestion in the ulcer area due to alteration in blood-flow. In effect he postulated that increased blood-flow, associated with increased secretion from the healthy gastric mucosa after the ingestion of food, would drain blood from the non-secreting ulcer-bearing area.

The experiences of 'Tom', Wolf and Wolff's subject (1947*a*), support the theory that pain is largely due to oedema and increased tissue tension. Normally the mucosa of his gastric fistula was insensitive to painful stimuli such as pinching or pricking, but on one occasion there was 'complete herniation of the stomach lining following an injury in a football game'. The mucosa became cyanotic and oedematous, and remained so for three or four hours. The pain was intense, and the mucosa was markedly tender to the slightest digital pressure. Again, when the mucosa of the stoma became red and oedematous after the use of a coarse rubber tube for feeding, the slightest touch with the tube became painful. Further, it is well known that pain can be produced by injecting normal saline into the bowel wall at a colostomy opening. Lastly, Dragstedt and Palmer (1931–2) reported the experiences of a patient who had a duodenal ulcer, and on whom a laparotomy was performed under local anaesthesia. Pinching of the ulcer area and traction on the scar of the ulcer visible on the external surface both caused pain; and, while traction was maintained, relief was produced by the injection into the duodenum of 20 ml. of a 5 per cent. solution of sodium bicarbonate.

Much, obviously, remains to be done before the origin of ulcer pain is satisfactorily explained. The present investigation is a repetition of the acidity and motility studies done by other workers, which, however, seems justifiable in view of their conflicting results. These studies were made during spontaneous attacks of pain, and the effects of introducing hydrochloric acid and sodium bicarbonate into the stomach and duodenum were observed.

Patients Investigated

Twenty-eight patients were used. All had typical peptic ulcer pain which was felt in the epigastrium, did not radiate, and was relieved by food and alkalis. A barium-meal examination was carried out in all cases except one. Sixteen patients were shown to have a duodenal ulcer. Three had an ulcer deformity of the duodenal cap, although no ulcer crater was demonstrated. Six others had a gastric ulcer in the lesser curvature, and one had prepyloric scarring. In one of the remaining two patients barium-meal examination was negative, and the other discharged himself from hospital before a radiological examination could be carried out. All except one of the 28 patients had felt pain during the 24 hours preceding an experiment. Spontaneously occurring attacks of pain were studied in 17 of the patients. Twenty had injections of hydrochloric acid, and 15 had injections of sodium bicarbonate, into the stomach or duodenum. Many were subjected to more than one type of experiment.

Method

A balloon-kymograph technique was used to record gastric and duodenal motility. The apparatus consisted of a radio-opaque Miller–Abbott tube, which was connected to a U-shaped water manometer, in one limb of which floated an ink writing device. The ink writer wrote on the drum of an electrically driven kymograph, fitted with an attachment which supplied a strip of paper long enough for a record lasting for several hours. A latex-rubber condom was tied to the end of the Miller–Abbott tube; the distal part of the condom projected beyond the end of the tube, and was filled with 6 ml. of mercury. The proximal part of the condom was tied over the tube, to form a balloon which could be inflated with air through the appropriate lumen of the tube. The balloon was two inches long, and the system held 40 ml. of air without distension. Changes of pressure in the balloon caused the float recorder to move up and down in the water manometer, and in this way, when the balloon was in position in the stomach or duodenum, a record of motility was obtained. Several holes were made in the second lumen of the Miller–Abbott tube just proximal to the balloon, so that gastric or duodenal contents could be aspirated for studies of acidity. In a number of the experiments a Ryle's tube was tied to the Miller–Abbott tube so that, when the aspiration holes of the latter lay in the first or second part of the duodenum, those of the former lay in the antrum, or in the lower part of the body of the stomach. Thus fluid could be introduced into, or aspirated from, both stomach and duodenum, simultaneously with the recording of duo-

denal motility. Experiments were carried out in the morning, the patients having fasted since the previous evening except for a cup of tea at 6 a.m. The soft palate and oropharynx were sprayed with 2 ml. of 2 per cent. xylocaine hydrochloride. After a few minutes, when the anaesthetic had taken effect, the patient swallowed the tube, and then lay on his right side for 45 to 60 minutes, to allow the weight of the mercury to carry the end of the Miller–Abbott tube towards and through the pylorus. At the end of an hour the patient was screened, and in nearly 60 per cent. of cases the end of the tube had by then reached the duodenum. When the balloon was inflated with air it could be seen as a translucency on the screen, and its position in the stomach and duodenum ascertained. Once it had attained the desired position, the Miller–Abbott tube was connected to the water manometer, and the balloon was inflated with air—20 ml. in the system for duodenal records, and 40 ml. for gastric records. During the recording the patient lay comfortably on his back and read a book. He made a signal at the onset or disappearance of pain.

Results

Spontaneous pain. Seventeen of the patients experienced pain which was identical with that from which they habitually suffered. Fourteen of these patients had a lesion of the duodenum, either proved by X-ray (ulcer in 11 cases, ulcer-deformity of the cap in two cases) or assumed from the history (one case); three had a gastric ulcer. To illustrate some of the points made in succeeding paragraphs, abbreviated protocols are given for three patients (Cases 3, 4, and 16; page 400), and reproductions of parts of the actual motility tracings are given for two patients (Cases 1 and 8). A line indicating the level of free acid in the gastric juice has been superimposed on the motility tracings. From a study of the records it is evident that there was no constant relationship between either acidity or motility and pain. Furthermore, pain sometimes occurred in the absence of free acid or motor activity.

To take the acidity results first: two patients (Cases 3 and 8; page 400 and Fig. 2) felt pain when there was no free acid in the gastric juice. In Case 8 there were repeated spasms of pain during two periods of achlorhydria which lasted 38 minutes and 51 minutes. In Case 3 pain recurred when the free acid level was zero, 21 minutes after the injection into the stomach of sodium bicarbonate. Both these patients had duodenal ulcers. Pain disappeared in five patients, including Cases 3 and 4 (see page 400), although the level of free acid remained, for periods of 4, 6, 10, 20, and 28 minutes respectively, at or near the maximum recorded during the preceding attack. Furthermore, two patients, including Case 3 (page 400), whose pain ceased at one level of acidity, had a recurrence of pain soon after when the acidity was appreciably lower. In another patient pain returned when the acidity was unchanged. On the other hand, there was no return of pain in one patient when the acidity rose again to levels which had previously been associated with pain. In yet another patient a free HCl level in the gastric juice of 2·0 mg. per ml. or more caused no pain in 30 minutes, but later a similar degree of acidity was associated with pain after only 21 minutes.

The evidence was not entirely against the view that acidity levels and pain are related. There was good correlation between the two in three patients, and fair correlation in four, including Case 16 (see below).

Spasms of pain coincided with individual duodenal contractions in two patients (Case 3, see below; Case 8, Fig. 2). Apart from these cases pain and motor activity were not closely related, and these same two patients felt other spasms of pain which did not coincide with contractions. Five patients, including Case 16, became free from pain while the motor activity continued to be as vigorous as before. Four others, including Case 1 (Fig. 1) and Case 4 (see above), experienced pain when motor activity was lowest, and often had none when it was highest. Finally, four patients, including Case 4, suffered discomfort during periods of complete or almost complete quiescence.

Case 3. Duodenal ulcer. Duodenal motility recorded

Time	*Free acid in gastric juice (mg.HCl/ml.)*	*Motility*	*Pain*
10.41 a.m.	..	+++	−
10.43	..	++	+
10.45	2·0	++	+
10.51	..	+++	+
10.56	2·0	+++	+
10.56½	..	+++C=	+Spasm
11.01	..	+++C=	+Spasm
11·03	2·65	+++	+
11.04	..	+++C=	+Spasm
11.09	..	+++C=	+Spasm
11.10	2·75	++	+
11.15	2·7	++	+
11.20	..	++	+Spasm
11.21	..	++	−
11.25	2·7	++	−
11.35	2·45	++	−
11.37	..	++	+
11.39	2·2	++	−
11.42	..	++	+Spasm
11.44	..	+++C=	+Spasm
11.46	2·45	+++	+
11.47½	..	+++C=	+Spasm
11.50	..	+++C=	+Spasm
11.51	2·25	+++C=	+Spasm
11.55	1·35	+++	+
11.58	..	+	+
12.00	..	+	+Spasm
12.02 p.m.	..	+	−
12.03	1·9	+	−
12.07½	..	+	+Spasm
12.08	..	+	−
12.09	..	+	+Spasm
12.10	..	+	−
12.11	2·65	+	−
12·20	2·2	−	−
12.23	..	++	−
12.27	2·05	++	−
12.28–31	$NaHCO_3$ 60 ml. into stomach		
12.30	..	++	+
12.39	0	++	+
12.40	..	++	−
12.51	0	++	−
12.52½	..	++C=	+Spasm
12.53	..	++	−
12.55	..	++	+
12.56	0	++	+

C = individual contraction coinciding with spasm of pain.

Case 4. Duodenal cap deformity. Duodenal motility recorded

Time	*Free acid in gastric juice (mg.HCl/ml.)*	*Motility*	*Pain*
10.36 a.m.	..	+++	−
10.50	2·5	+++	−
10.56	..	++	−
10.57	..	++	+
11.00	2·7	++	+
11.04	..	+	+
11.08	Homatropine methylbromide 2 mg. intravenous		
11.10	2·75	±	+
11.20	2·7	±	−
11.30	2·8	−	−
11.40	2·7	−	−
11.44	..	−	+
11.46½	..	+	+
11.48	2·75	+	+
11.55	2·65	+	+
12.00	2·5	+	+
12.05 p.m.	2·3	+	+
12.06	..	−	+
12.08	..	−	−
12.10	2·15	−	−
12.14	..	+	−

Case 16. Gastric ulcer. Gastric motility recorded

Time	*Free acid in gastric juice (mg.HCl/ml.)*	*Motility*	*Pain*
10.33 a.m.	..	++	+
10.41	0·4	++	+
10.51	0	++	+
11.01	0	++	+
11.06	..	++	−
11.12	0	++	−
11.20	0·1	++	−
11.30	0·45	++	−
11.37	..	++	+
11.40	0·5	++	+
11.44	..	++	−
11.46	..	++	+
11.50	0·35	++	+
11.53	Methanthelinium bromide 25 mg. intravenous		
11.54	..	+	+
12.00	0·6	+	+
12.04 p.m.	0·6	+	+
12.07	..	+	−
12.13	0·55	+	−

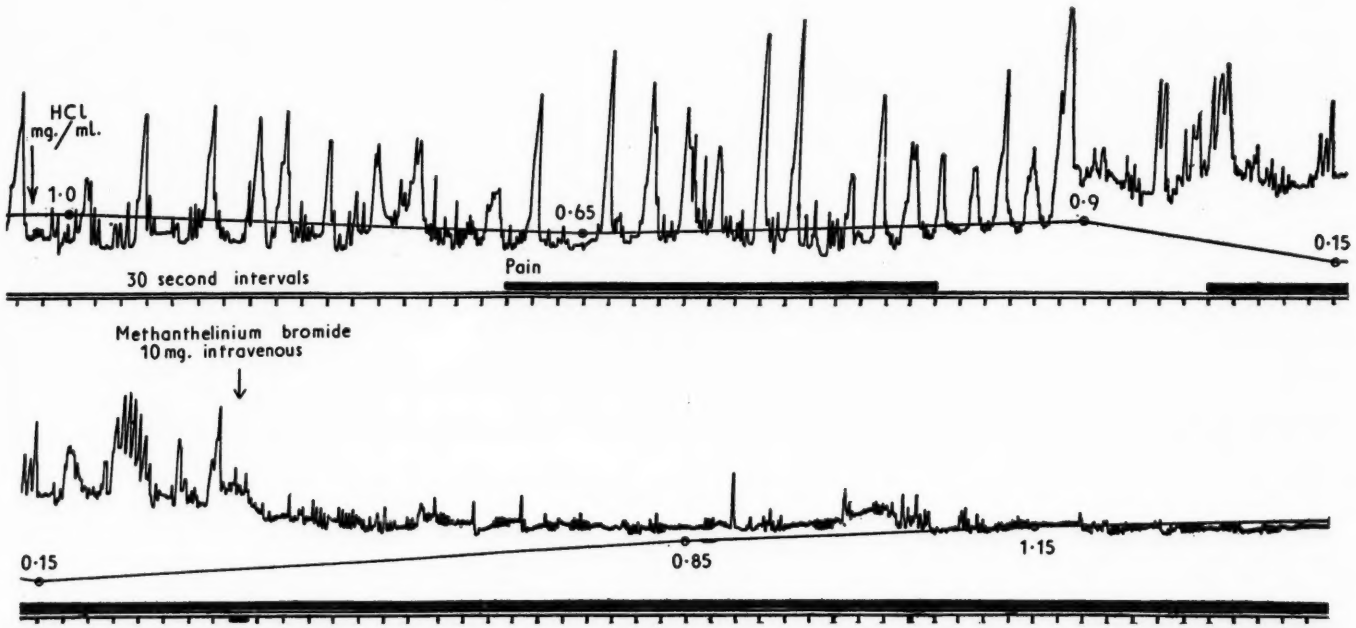

FIG. 1. Case 1. Ulcer deformity of the duodenal cap. Record of duodenal motility, with a superimposed line indicating the level of free HCl in mg. per ml. of gastric juice. Pain was intermittent at first, although motility was continuously vigorous, consisting of Type III contractions (Code, Hightower, and Morlock, 1952). During the latter part of the record there was continuous pain, although motility was at its lowest. The first attack of pain began when the acid level was falling, and stopped when it was rising. The second attack began when the acidity was again falling.

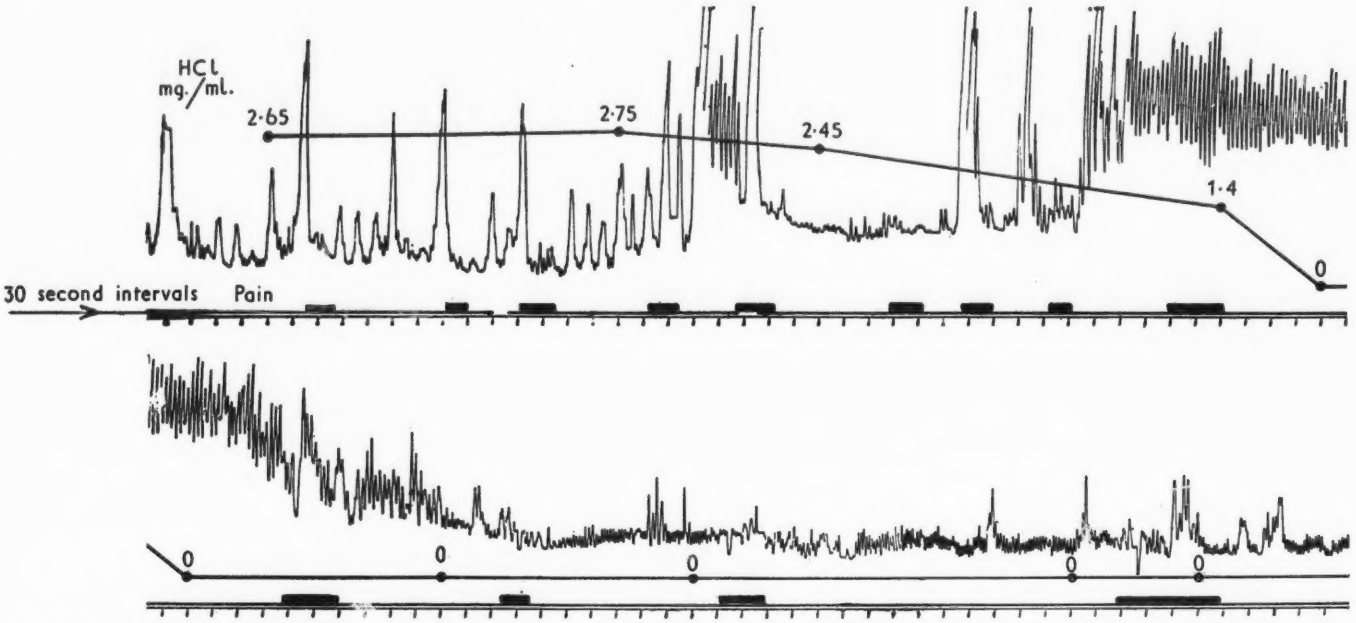

FIG. 2. Case 8. Duodenal ulcer. Record of duodenal motility, showing a number of spasms of pain coinciding with powerful peristaltic (Type III) waves. Other spasms of pain were noted when motor activity was slight. The prolonged Type III contraction occurring in the middle of the record and lasting six minutes ('duodenal tetanus') was associated with pain which lasted only one minute and stopped before the end of the contraction. Four attacks of pain occurred during a period of achlorhydria, two of them when motility was slight. There was no bile in the gastric juice at this time.

The opportunity was taken to observe the effect on pain of injections of methanthelinium bromide (Cases 1, 2, 7, 14, 15, and 16), atropine sulphate (Case 9), and homatropine methylbromide (Case 4) (Table I). The drugs were given intravenously during attacks of pain. Three patients did not experience any relief, but in the other five pain stopped five, nine, nine, 12, and 14 minutes respectively after the injection. The interpretation of these results is difficult.

TABLE I

Effect of Intravenous Antispasmodic Drugs on Ulcer Pain

Case number	*Drug*	*Gastric acidity*	*Motility*	*Pain*
1	Methanthelinium bromide (banthine) 10 mg.	Increased	Greatly reduced	Unchanged
2	,, ,, 10 mg.	Unchanged	,, ,,	Unchanged
7	,, ,, 10 mg.	Slightly reduced	,, ,,	Stopped after 9 min.
14	,, ,, 25 mg.	Reduced	,, ,,	Stopped after 5 min.
15	,, ,, 25 mg.	Unchanged	,, ,,	Stopped after 9 min.
16	,, ,, 25 mg.	Increased	,, ,,	Stopped after 14 min.
9	Atropine sulphate 1·3 mg.	Slightly increased	,, ,,	Unchanged
4	Homatropine methylbromide 2·0 mg.	Unchanged	,, ,,	Stopped after 12 min.

Motility was greatly reduced in every case almost immediately after administration of the anticholinergic drug, but there was then an appreciable delay of up to 14 minutes before the cessation of pain. The acidity of the gastric juice remained unaltered in two of the patients whose pain was relieved. In two it decreased, and in one it increased. There was effective depression of motility in the three patients who continued to have pain. The degree of acidity did not alter in one, but in the other two it increased after the injection.

Artificially induced pain. Hydrochloric acid, 100 ml. of 0·5 per cent. solution, was injected slowly into the stomach in 19 patients (Table II). The injections lasted five minutes. Fifteen patients developed pain, 12 after a single injection and three more after a second injection given 12, 18, and 33 minutes after the first. Six of the patients had a gastric ulcer, and all of these developed pain. Thirteen had a duodenal lesion, and of these nine developed pain. Four patients were quite unaffected by the introduction of acid, but one of these was in a pain-insensitive phase as defined by Palmer (1926*b*). It is interesting to note that two patients, who experienced pain after the first injection of acid, felt none after a second injection given 12 and 18 minutes later respectively. The pain which followed the injection of acid was generally of the usual ulcer type, but it varied considerably in severity as compared with that which the patient felt spontaneously. Occasionally it was 'burning' in character. The average interval between the injection of acid into the stomach and the onset of pain was 8·8 minutes (three to 14 minutes) in cases of gastric ulcer and 7·2 minutes (one to 18 minutes) in cases of duodenal ulcer—an unexpected result.

Hydrochloric acid 0·5 per cent. was injected directly into the duodenum in five patients who had scarring or ulceration of the duodenum (Table III). The

volume of acid which was used ranged from 30 to 100 ml. Pain occurred in each case one to 10 minutes after the injection (average three and a half minutes). Acid was later injected into the stomach of one of these patients, and no pain occurred, although the duodenal injection had produced pain within one and a

TABLE II

Incidence of Pain after Injection of 0·5 per cent. HCl 100 ml. into the Stomach

		First injection		*Second injection*	
Case number	*Lesion*	*Pain*	*Interval between injection and onset of pain (minutes)*	*Pain*	*Interval between injection and onset of pain (minutes)*
1	Duodenal cap deformity	—	..	+	8
6	Duodenal ulcer	—	..	..	Not given
7	Duodenal ulcer	—	..	..	Not given
11	? Duodenal ulcer No X-ray	+	10	+	7½
12	Duodenal ulcer	+	6½	..	Not given
13	Duodenal ulcer	+	10½	—	..
15	Gastric ulcer	+	14	..	Not given
16	Gastric ulcer	+	4½	—	..
17	Gastric ulcer	+	14	..	Not given
18	Duodenal ulcer	+	6	—	..
19	Duodenal ulcer	+	1	+	1
20	Duodenal ulcer	—	..	..	Not given
21	Duodenal ulcer	—	..	..	Not given
22	? Duodenal ulcer	+	18	..	Not given
23	Duodenal ulcer	+	6½	..	Not given
24	Duodenal ulcer	+	4½	..	Not given
25	Gastric ulcer	—	..	+	5
26	Gastric ulcer	—	..	+	13
27	Gastric ulcer	+	3	..	Not given

TABLE III

Incidence of Pain after Injection of 0·5 per cent. HCl 30–100 ml. into the Duodenum

		First injection		*Second injection*	
Case number	*Lesion*	*Pain*	*Interval between injection and onset of pain (minutes)*	*Pain*	*Interval between injection and onset of pain (minutes)*
1	Duodenal cap deformity	+	2	..	Not given
4	Duodenal cap deformity	+	2	..	Not given
6	Duodenal ulcer	—	..	+	10
7	Duodenal ulcer	+	1½	..	Not given
11	No X-ray ? Duodenal ulcer	+	1	..	Not given

half minutes. In two other patients it was found that injection of acid into the duodenum produced pain more quickly than did injection into the stomach; intraduodenal injections produced pain in two minutes or less, whereas intragastric injections produced pain after seven and a half and eight minutes.

The effect of hydrochloric acid on gastroduodenal motility. It has been suggested

that hydrochloric acid causes pain by increasing gastroduodenal motility (Kinsella, 1948), but the present investigation did not confirm this view. Thirty-three injections of hydrochloric acid were made into the stomach and duodenum (Table IV) and, although 60 per cent. of these produced an increase in motility, 36 per cent. of the pain-producing injections were not associated with any increase in motor activity.

The effect of sodium bicarbonate on motility. Sodium bicarbonate, 30 to 60 ml. of 9 per cent. solution, was injected into the stomach on 18 occasions. This was

TABLE IV

Incidence of Pain and Increased Motor Activity ('Spasm') after Injection of 0·5 per cent. HCl into the Stomach and Duodenum

	Total number of injections	*Pain only*	*'Spasm' only*	*Pain and 'spasm'*
Stomach . . .	27	7	6	10
Duodenum . . .	6	1	0	4

invariably followed by relief of pain, although on nine occasions there was an increase in motor activity, which in two cases amounted to duodenal spasm lasting for six to seven minutes. Six injections were made into the duodenum, and two were followed by increased tone and movement. Again pain was relieved in spite of the increased motility. These observations are at variance with the view that alkalis relieve pain by relaxing the postural tone of the stomach and duodenum (Carman, 1920). The average delay between the introduction of sodium bicarbonate and the relief of pain was nine minutes (one to 23 minutes).

Discussion

It is clear from the foregoing experiments that the pain of peptic ulceration cannot be satisfactorily explained by relating it solely to changes in the acidity of the stomach contents, or to the varying degrees of the muscular activity of the stomach or duodenum. Fundamental to the acid theory is the assumption that pain does not occur in the absence of free acid, and the first point of interest in the present studies is the undoubted occurrence of repeated attacks of pain in one patient in the absence of any free acid. Another patient felt a spasm of pain shortly after the gastric contents had been rendered alkaline with sodium bicarbonate. Although it is true of the remaining 15 patients to say that pain was experienced only when acid was to be found in the gastric juice, this fact does not greatly help in any attempt to explain the onset and disappearance of individual attacks of pain. Only three of the 17 patients had attacks which could be closely correlated with changes in acidity, and four others had attacks which showed only partial correlation. The remainder, over 50 per cent., had symptoms which could not be related to levels of acidity. Thus pain would disappear for a time, and then return, while the acidity remained unchanged or even fell to a lower level than before. Degrees of acidity which in the early part of a record had given rise to pain sometimes failed to produce any discomfort at all during

the later parts of the record. Examination of the experiments with spontaneous pain does not, then, offer much support for the acid theory. On the other hand there is no doubt that, as Palmer (1926*b*, 1927), Palmer and Heinz (1934), and Bonney and Pickering (1946–8) have previously shown, the injection of hydrochloric acid into the stomach caused pain which could be relieved by neutralizing the stomach contents. An indication that the acid was having a local effect on the ulcer was given by the observation, in two cases of duodenal ulceration, that pain took appreciably longer to develop when the acid was injected into the stomach instead of into the duodenum. The view that acid might cause pain by stimulating an increase in motility has not been substantiated, nor was the relief of pain after the administration of alkali found to be the result of any depression of muscular activity. The correlation between pain and motor activity was poor. Thus, although spasms of pain were occasionally observed to coincide with prominent individual contractions of the duodenum, this finding was exceptional. Generally it was difficult to relate pain to motility, and it was not uncommonly observed in the absence of contractions. Every possible combination was found: violent activity with no pain, violent activity continuing incessantly while pain was intermittent, and pain without muscular activity. Spasmodic colicky pain was in fact the only kind of pain which could be correlated with motility, and this of course is much less common in peptic ulcer than constant aching pain. There are many objections to both the acidity and the motility theories, and it is obvious when considering the results that the sensitivity of the ulcer is much more important than any particular level of acid or degree of motility. If pain comes and goes while acidity and motility remain unchanged, then the variable factor is likely to be intimately connected with the ulcer itself. Since the changes in sensitivity take place frequently and rapidly, they can hardly represent healing processes, but might well be due to variations in the degree of oedema and engorgement of the ulcer area, these variations in turn being due to alterations in the blood-flow, as Kinsella has suggested. Quite mild stimuli, such as a low level of acid, minor muscular activity, or even the jet of the gastric contents projected against it, may be noxious to a sensitive ulcer. Only by putting the emphasis on the local inflammatory reaction and the sensitivity of the ulcer can one attempt to explain the pain of peptic ulceration satisfactorily.

I am indebted to Professor Dunlop for his help and encouragement, and for his permission to carry out the investigations on his patients.

Summary

1. The origin of the pain of peptic ulceration is discussed, and the literature reviewed.

2. A balloon-kymograph technique has been used in a study of the relationship between pain and motility and acidity in 28 patients, all of whom had symptoms of peptic ulceration. The majority had a demonstrable ulcer crater or ulcer deformity.

3. Spontaneous attacks of pain occurred in 17 of the patients. No constant relationship was found either between acidity and pain or between motility and pain.

4. Hydrochloric acid, 0·5 per cent., was injected into the stomach of 19 of the patients, and 15 developed pain after an average delay of 8·8 minutes in cases of gastric ulcer and 7·2 minutes in cases of duodenal ulcer. Injection of hydrochloric acid into the duodenum of five patients produced pain in each case after an average delay of three and a half minutes.

5. Sodium bicarbonate, 9 per cent., was injected into the stomach or duodenum on 24 occasions. Pain was relieved after an average delay of nine minutes.

6. The production of pain by hydrochloric acid, and its relief by sodium bicarbonate, could not be correlated with changes in motility.

7. The effect of antispasmodic drugs on pain was observed in eight cases.

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THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1955

FORTY-NINTH ANNUAL GENERAL MEETING

THE FORTY-NINTH ANNUAL GENERAL MEETING was held in Manchester on Friday and Saturday, May 27 and 28 in the Lesser Free Trade Hall. The attendance book was signed by 219 members and 43 visitors. The proceedings began at 9.30 a.m.

The President, Professor V. M. Synge, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read, confirmed, and signed. The election of Officers, Executive Committee, Honorary Members, and Ordinary Members then followed.

Executive Committee

President.	Professor J. Crighton Bramwell.
President-Elect.	Sir W. Russell Brain, Bt.
Treasurer.	Dr. C. Newman.
Secretary.	Dr. C. M. Fletcher.
Members for England and Wales.	Dr. E. N. Chamberlain. Professor A. P. Thomson. Dr. E. R. Boland. Professor G. W. Pickering. Dr. E. E. Pochin. Professor H. Scarborough.
Members for Scotland.	Professor I. G. W. Hill. Dr. J. G. M. Hamilton. Dr. A. A. F. Peel.
Members for Ireland.	Dr. R. W. M. Strain. Professor G. M. Bull. Dr. L. K. Malley.

Election of Honorary Members

Sir Harold Boldero.
Professor David Campbell.
Professor Philip C. P. Cloake.
Dr. W. R. Snodgrass.
Professor A. P. Thomson.

Election of Ordinary Members

Edward Miller Buzzard, F.R.C.P., Physician, United Oxford Hospitals and Oxford Region.

Archibald Leman Cochrane, M.B., D.P.H., Epidemiologist, Pneumoconiosis Research Unit, Cardiff.

Paul Henderson Davison, M.D., M.R.C.P., Assistant Physician, United Birmingham Hospitals.

Peter Gatenby, M.D., M.R.C.P., Physician, Dr. Steevens' and Rotunda Hospitals, Dublin.

Robert Roland Hughes, M.D., M.R.C.P., Physician, Royal Liverpool United Hospitals.

Anthony Howard James, D.M., M.R.C.P., Senior Lecturer in Medicine, University of Wales.

Aubrey Leatham, M.R.C.P., Assistant Physician, St. George's Hospital.

John Marshall Ledingham, M.D., M.R.C.P., Reader in Medicine, The London Hospital.

Kenneth Gordon Lowe, M.D., M.R.C.P., Senior Lecturer in Medicine, University of St. Andrews.

Reginald William Luxton, M.D., F.R.C.P., Lecturer in Medicine, University of Manchester.

Edward McCombie McGirr, M.R.C.P., Lecturer in Medicine, University of Glasgow.

Alastair Goold Macgregor, M.D., M.R.C.P., Senior Lecturer in Therapeutics, University of Edinburgh.

William Neville Mann, M.D., F.R.C.P., Physician, Guy's Hospital.

Frederick John William Miller, M.D., M.R.C.P., Lecturer in Paediatrics, University of Durham.

Desmond Alan Dill Montgomery, M.D., M.R.C.P., Physician, Royal Victoria Hospital, Belfast.

Campion Aubrey Rumball, F.R.C.P., Air Commodore, R.A.F., Consultant in Medicine.

George Geoffrey Evanson Smyth, M.D., F.R.C.P., Physician, Manchester Royal Infirmary.

William Whitaker, M.D., M.R.C.P., Senior Lecturer in Medicine, University of Sheffield.

The Secretary presented the Treasurer's report for 1954, because the Treasurer, Dr. Charles Newman, had been prevented by illness from attending the meeting. There was an opening balance of £805 and a closing balance of £855. The smaller profit for the year was accounted for by the extra expenditure on the *Quarterly Journal of Medicine*. Dr. A. M. Cooke, speaking on behalf of the editorial board of the Journal, expressed the regret of the editors and of the Clarendon Press that an increase in price was necessary. He pointed out that since 1938 printing charges had increased by 160 per cent. and the cost of paper by 225 per cent., whereas the increase in price of the Journal from 35*s*. in 1938 to 50*s*. at the present time was an increase of only a little more than 40 per cent. He also pointed out that, even with the increase, the price of the Journal was low in comparison with similar publications. The accounts were adopted by the Association.

The Association agreed to amend the wording of Rule 15 by adding the words 'or at' after 'before' at the top of page 6 in the list of rules. The Association agreed to amend Rule 17 by adding the words 'A summary of the proceedings of the meetings shall be published in the *Quarterly Journal of Medicine*.'

The proposal of the Executive Committee to amend Rule 18 to define the number of guests that might be admitted at the Annual Dinner provoked considerable discussion, in which Professor L. J. Witts, Professor J. Crighton Bramwell, Dr. C. Hardwick, Dr. George Graham, Professor J. McMichael, and Dr. K. Robson spoke. The question was referred back to the Executive Committee, the general opinion being that the number of official guests should be defined, that only one communicant for each paper at the proceedings should attend the dinner, and that no more than a few local registrars who had assisted in demonstrations should be invited at the discretion of the President. It was reported that the Manchester members had invited 30 demonstrators to attend the dinner, but proposed to pay for the dinners themselves. Dr. Maurice Campbell proposed and Dr. Douthwaite seconded a proposal that the Association should pay for these guests. On a show of hands the proposal was defeated by a large majority.

Place of Meeting, 1956 and 1957. It was confirmed that the 1956 meeting should be held in London. Dr. Rae Gilchrist invited the Association to meet in Edinburgh in 1957. The invitation was accepted.

Professor J. Crighton Bramwell then took the Chair. He thanked Professor Synge for his services to the Association during his year of presidency.

SCIENTIFIC BUSINESS

Friday Morning, May 27

1. Dr. W. Brockbank gave a talk on the *Manchester Medical School*. He said that teaching started in 1753 with the appointment of John Daniel as apprentice to the Apothecary at the Infirmary. The first lectures in medical subjects were given by Charles White in 1783, and these became a regular feature. Apprentices were admitted to the Infirmary in ever-increasing numbers. The first medical school was founded by Joseph Jordan in 1814 at his own house. At this time attendance at lectures in London was obligatory for qualification, until Jordan's initiative and persistence led to his lectures on anatomy and surgery being accepted by the Society of Apothecaries in 1821. A second school was founded by Thomas Turner in 1824. It was the first complete medical school in Manchester and the provinces, and was the only one to receive the royal accolade. Clinical teaching was recognized in 1834, when a student could do all his work in Manchester, but had to go outside for his diplomas. Two other schools were founded, in Marsden

Street (1829) and Chatham Street (1850). All four schools were private ventures, and all were eventually absorbed into the Royal School. Chatham Street boasted a well-lighted dissecting room, in contrast to that at the Royal School where dissection had to be done by gas-light even at midday. The University was founded in 1851 by John Owens, being known as Owens College. The College was without a medical school until 1872, when it acquired the Royal School. Two years later it was transferred to the present medical school building in the newly built college. University status was granted in 1880, and in 1883 medical degrees were conferred for the first time. The University was upgraded in 1903, and became the Victoria University of Manchester. Five years later the Royal Infirmary moved to its present site, five minutes' walk from the University. Since then both had gone from strength to strength, except for the fabric of the Infirmary, not yet fifty years old, which was causing grave concern.

2. Dr. P. Hugh-Jones (introduced) described *Diabetes in Jamaica* against a social background of poverty, widely different dietary habits, and the consumption of local herb remedies such as 'bush teas'. Experience in the diabetic clinic of the new Hospital of the University of the West Indies (U.C.W.I.) showed that it was possible to teach the patients to control their diabetes and give their own insulin injections when necessary, after appropriate local diet sheets had been produced. An analysis of 215 consecutive diabetic patients attending the hospital during an 18-month period showed that the two main types seen elsewhere predominated: Type 1, of early-age onset, insulin-sensitive and developing ketosis without insulin, and Type 2, of later onset, insulin-resistant, tending to obesity but not to ketosis except during infections. This analysis also revealed a third variety, Type 'J', not hitherto described. These patients had diabetes of early onset; they were thin, but were insulin-resistant, and seldom showed ketosis even without insulin. Analysis of diets before the onset of diabetes showed a tendency to high calorie intake only in Type 2 diabetes. Liver biopsy in a very few subjects showed fatty livers in Type 2, but normal histology in Types 1 and 'J'. The complications of diabetes and the prevalence of hypertension were similar to those found in temperate zones. In a few instances established diabetes in young subjects had apparently remitted spontaneously for long periods.

Dr. W. G. Oakley said that he had noticed the unusual feature of some young Jamaican diabetics, attending his clinic in this country, not relapsing, as he would have expected, when they stopped their insulin, and supposed that they were examples of Type 'J'; he also asked whether there was any evidence of over-production of growth hormone, such as a change in skeletal growth relative to age, in this type of diabetes. He thought that, in view of the fact that the diabetes appeared to have cleared up completely in a few cases, the disease seemed to be quite different from that commonly observed in young people in this country and, this being the case, deserved fuller investigation.

Professor R. B. Hunter asked for more information about the 'bush-teas' used in Jamaica for the treatment of diabetes.

Professor A. V. Neale inquired whether there was any information about the genetics of diabetes mellitus in Jamaica.

Dr. D. K. O'Donovan asked whether the patients whose insulin requirement had diminished were also suffering from severe malnutrition. If so, such patients might subsequently need increased doses of insulin. He had seen two such patients—both male adolescents—whose insulin increase was correlated with increasing adrenal activity.

In reply, Dr. Hugh-Jones said that the very high rate of illegitimacy precluded studies of inheritance. No special study had been made of skeletal growth, but it did not appear to be abnormal, Type 'J' patients being of normal build and development apart from their thinness; some of them had severe malnutrition. The 'bush-teas' were most interesting. The Botany Department (U.C.W.I.) had published in the *West Indian Medical Journal* an extensive list of the different plants used for various purposes. He had himself made preliminary studies with three of those most commonly used and reputed to cure diabetes, namely 'periwinkle', 'mistletoe', and 'Nicol berry'. Teas were prepared from these in the traditional manner. Preliminary trials on volunteers from the medical staff showed that larger doses than those usually taken produced no obvious ill effects. They were then given to diabetic volunteers, who had been previously 'stabilized' on a standard diet so as to have a consistent pattern of fairly severe glycosuria and hyperglycaemia throughout the day. None of the herbs produced hypoglycaemia, but periwinkle and mistletoe, in some cases, appeared to alter the renal threshold, reducing the amount of sugar in the urine. This suggestion needed confirmation. Perhaps more interesting was the effect of Ackee (*Blighia sapida*), which could produce definite hypoglycaemia. A local condition called

'vomiting sickness', which was associated with sudden coma and was often fatal in undernourished Jamaican children, had been found by the Department of Medicine to be a true hypoglycaemia; subsequently the Department of Chemistry had shown that extracts of Ackee seeds (the aril was commonly eaten in Jamaica) contained fractions, separable by chromatography, which could cause a fatal hypoglycaemia in animals, and which might be a cause of 'vomiting sickness'. These extracts had not been given to diabetic patients because they were not available in sufficient quantities, because they might be toxic, and because the plant was not regularly used by patients as a diabetic 'cure'.

3. Dr. H. T. Howat and Drs. P. R. Duncan, A. A. Harper, S. Oleesky, J. E. Scott, Josephine Smith, and H. Varley (introduced) discussed the *Clinical Significance of Changes in Serum Amylase and Lipase in Man after Stimulating the Pancreas with Secretin and Pancreozymin*. They stated that early in acute pancreatitis elevated values of serum amylase and lipase were found in the majority of patients, but that in the diagnosis of chronic pancreatic disease, particularly of carcinoma of the pancreas, these estimations were of little help. Several workers had therefore tried to increase the sensitivity of these tests by stimulating the pancreas to secrete, using secretin. The interpretation of these tests was considerably affected by the question whether or not morphine had been given. A second substance, distinct from secretin, had been separated from extracts of duodenal mucosa by Harper and Raper in Manchester in 1943. This extract, which increased the enzyme output of the pancreas, they had named pancreozymin. The authors had been investigating the physiological properties of pancreozymin in man during the past five years, and had observed the effect of stimulating the pancreas with secretin and pancreozymin upon serum enzyme values both in health and in disease. Significant increases of the serum amylase and lipase had been found in chronic pancreatic disease and carcinoma of the pancreas, so long as sufficient pancreatic tissue remained active. In their hands the glucose-tolerance test had proved of value in assessing the extent of pancreatic damage. When the glucose tolerance was impaired owing to pancreatic damage, elevated enzyme values were less often found after stimulation. These tests were complementary, and used together were of value in estimating pancreatic involvement in chronic pancreatitis and carcinoma of the pancreas. This secretin-pancreozymin test was positive in some cases of biliary-tract disease, and occasionally after recovery from acute pancreatitis. The significance of these findings in individual patients was discussed.

Dr. J. D. Nabarro inquired about the relative sensitivity of the tests.

Dr. M. D. Milne asked whether there was any physiological explanation for the more pronounced increase of serum enzymes in cases of pancreatic neoplasm uncomplicated by diabetes.

Dr. A. H. Douthwaite inquired about the dose of morphine used in experiments on pancreatic function. In the 30 per cent. of cases in which no rise of serum amylase followed morphine administration, was the dose repeated? If so, how often? The point was of interest in view of a morphine addict seen recently with deep epigastric pain and a serum amylase of 800 units. Laparotomy revealed no disease. Withdrawal of morphine restored the amylase level to normal. A diagnostic hazard was thus revealed.

In reply, Dr. Howat stated that impaired glucose tolerance seemed to provide a means of assessing the extent of pancreatic damage in the severer degrees of chronic pancreatitis and chronic relapsing pancreatitis. A similar degree of impairment of glucose tolerance occurred in many cases of carcinoma of the pancreas; this impairment seemed to be an index of the extent of acinar destruction. In the presence of impaired glucose tolerance these stimulation tests were, therefore, less likely to be positive. He could not answer Dr. Douthwaite's question, since he had not made a personal study of the use of morphine in conjunction with pancreatic stimulation. He would agree, however, that care should be taken in interpreting enzyme values in serum obtained after morphine had been given, especially in acute abdominal emergencies.

4. Dr. J. Innes and Mr. A. I. S. Macpherson and Dr. J. A. Owen (introduced) described the *Changes in the Peripheral Blood before and after Operation for Portal Hypertension*. In this syndrome alimentary haemorrhage might produce iron-deficiency anaemia, and the presence of an enlarged and over-active spleen might lead to leucopenia and thrombocytopenia. Studies of the peripheral blood before and after operation in 58 cases had shown that the anaemia might be improved by operative procedures which lessened the incidence of bleeding from cardio-oesophageal veins, and by oral iron therapy. Leucopenia and thrombocytopenia remained materially unaffected by measures such as portocaval anastomosis or splenic arterial ligation, and were only corrected if splenectomy was included in the operation. In 34 cases in which splenectomy had been carried out and the

patients had been followed up for five years or more after operation, significant overall improvement in the blood picture had been well maintained. The evidence suggested that the enlarged spleen had been responsible for the pre-operative leucopenia and thrombocytopenia, but it appeared to have played little or no part in the production of anaemia. Improvement in the latter could be ascribed to the administration of iron and to the effects of surgery in reducing the frequency and severity of alimentary bleeding.

DR. SHEILA SHERLOCK said that in fifty patients with cirrhosis, in whom measurements of the portal venous pressure were available, there was no correlation between the height of the portal venous pressure and the total leucocyte or platelet count. It was not surprising, therefore, that reduction of the portal pressure by portocaval anastomosis had little effect on the blood picture. Although leucopenia and thrombocytopenia were common in patients with cirrhosis, it might be questioned whether they caused symptoms and were an indication for operation. Splenectomy was followed by an increase of platelets and leucocytes, but anaemia was unaffected. Splenectomy led to the division of valuable portal-systemic collaterals in the lieno-renal and lumbar region, and the splenic and portal veins might close by thrombosis, precluding future portocaval anastomosis. Dr. Sherlock asked what was the incidence of post-operative gastro-intestinal haemorrhage in the patients who had splenectomy compared with those who had a portocaval anastomosis or those untreated.

DR. INNES, in reply, agreed that evidence of hypersplenism *per se* did not in general justify splenectomy, and in the cases in which the spleen had been removed without establishing a portal-systemic venous anastomosis there had been indications other than the peripheral blood changes. A very large spleen might call for removal to prevent the risk of traumatic rupture and prevent frequent painful attacks of perisplenitis. In some of the cases thrombocytopenia had been associated with a bruising tendency which had been corrected by splenectomy, and other patients subject to repeated intercurrent respiratory infections had been much helped by the sustained post-splenectomy rise in their leucocyte count. It seemed that recurrence of haemorrhage from varices could occur after any operation where the varix-bearing area was not removed.

5. DR. J. D. SPILLANE described *The Effect of Nicotine in Spinocerebellar Ataxia*. Four patients with spinocerebellar ataxia had complained of the adverse effect of tobacco-smoking on their disability. The first three patients were suffering from progressive spinocerebellar degeneration, with onset of disability in the fifties. The fourth patient was probably one of disseminated sclerosis, starting at 17, with a progressive course and with basilar invagination. Smoking had had no effect before the onset of the disease, but now they had all found that smoking (cigarettes in three cases, pipe in one) aggravated their ataxia or ataxic dysarthria, or both. This was confirmed by observation. Nicotine was shown to be responsible by the effect of intravenous injection of nicotine acid tartrate (1 to 3 mg.). In Cases 1 and 2 this had a striking effect, rendering each patient grossly ataxic and nearly incomprehensible. Sound records and a cine-film were used to demonstrate these effects. In Cases 3 and 4 speech was not affected, but ataxia was increased. Syncope was not produced, nor was there loss of power or reflex activity. The patient might begin to feel the adverse effects before he had finished one cigarette, and they usually lasted 15 to 30 minutes. Other ganglion-blocking agents, such as curare, pitressin, or acetylcholine, had no adverse effect. Tobacco-smoking and nicotine injections had no adverse effect upon eight other cases of progressive spinocerebellar degeneration, nor upon some 20 patients suffering from various other organic diseases of the nervous system. It was thought that nicotine had a central action upon synaptic transmission of nerve impulses.

6. DR. F. R. FERGUSON, DR. L. A. LIVERSEDGE, and DR. E. C. HUTCHINSON (introduced) gave a *Review of 85 Cases of Myasthenia Gravis seen over the past 22 Years*. It was difficult to assess with certainty the relative values of thymectomy and medical treatment in the management of that condition, and there was some doubt concerning recent claims of the benefits of thymectomy. Over a period of 22 years 85 cases of proved myasthenia gravis had been seen at Manchester, and the survivors had been re-examined in the last three months of 1954. Of the 10 patients subjected to thymectomy six were dead, and the remaining four suffered disability of varying degrees. Of the 75 medically treated patients nine were dead, and six of the nine had undoubtedly died from their myasthenia. Two of these patients had a thymoma. Six others had not been traced, but the remaining 60 had all been seen. Forty-two of these 60 were fully working, and only two were incapable of working at all. Forty-four of the 85 cases had presented as ocular myasthenia, and 27 of these had remained exclusively ocular. Only one of these 27 patients had died (of carcinoma of the tongue). Comparison of remissions experienced by patients receiving neostigmine with those reported in the pre-neostigmine era had shown that neostigmine reduced neither the frequency nor the duration of remissions. Recognition of the special nature of the

ocular form of myasthenia was most important, since in this type thymectomy seemed inadvisable. The precise place of thymectomy, even in the more generalized form of the disease, was still debatable.

DR. S. WHITTAKER asked about the effect of pregnancy. He had seen one case in which pregnancy had twice caused a relapse.

DR. C. H. WHITTLE asked about the clinical features of the two cases of thymoma. These tumours must be very rare. He had seen only one case, and this presented with scattered secondary deposits in the skin. The patient, a man of 72, had had myasthenia gravis for 14 years, fully controlled by prostigmine. The skin lesions were granulomatous, and resembled leukaemic infiltration. Their relationship to the thymus was established only after the post-mortem examination, and when the histology had been closely studied. There were also secondary deposits in the lymph-glands, liver, kidneys, pleurae, and pericardium. Dr. Whittle also asked whether the risk of thymoma in myasthenia gravis was sufficient to affect the question of operative interference.

DR. A. C. DORNHORST asked whether the patient diagnosed clinically as having a thymoma, and who later developed cerebral metastases, might not have had a bronchial carcinoma. The association of the latter condition with myasthenia had been reported.

In reply DR. FERGUSON and DR. LIVERSEDGE stated that the course of myasthenia in pregnancy showed a great variation from case to case. Termination of the pregnancy was rarely indicated, but in one patient a very severe myasthenic crisis in the third month of pregnancy improved within 24 hours of its termination. They had not encountered any proven metastases in their cases of thymoma. The association of bronchial neoplasm with a myasthenic picture was recognized, but carcinomatous mediastinal tumours did not display the extraordinary sensitivity to radiotherapy shown by thymoma.

Luncheon was taken in the Great Hall of the Nurses' Home, Manchester Royal Infirmary. During the afternoon there were the following demonstrations at the Royal Infirmary, many of which were illustrated by photographs and diagrammatic displays produced and mounted by the Department of Medical Illustration under the direction of DR. ROBERT OLLERENSHAW:

Department of Haematology

Leukaemias. J. F. WILKINSON, M. C. G. ISRAELS, and B. J. LEONARD.
Haemorrhagic Diseases. J. F. WILKINSON, M. C. G. ISRAELS, and R. L. TURNER.

Department of Medicine

Retinal photographs in colour. D. SNOW, R. LAWTON, and ROBERT PLATT.
Renal osteodystrophy. S. W. STANBURY and J. BALL.
Mediastinal parathyroid adenomata. W. F. NICHOLSON and S. W. STANBURY.
Treatment of Type 2 nephritis with ACTH and cortisone. M. H. ROSCOE.

Dr. Howat's Clinic and the Department of Clinical Pathology

The use of cholecystokinin to assess gall-bladder function in man.
The use of secretin and pancreozymin to assess pancreatic function in man, by duodenal intubation and quantitative recovery of duodenal contents, and by serum enzyme studies. P. R. DUNCAN, A. A. HARPER, H. T. HOWAT, S. OLEESKY, J. E. SCOTT, JOSEPHINE SMITH, and H. VARLEY.

Department of Cardiology

The ballistocardiogram in coronary disease. E. G. WADE, R. M. FULTON, J. MACKINNON, and A. MORGAN JONES.
Technique of post-mortem examination of the heart in coronary disease. D. SNOW, A. MORGAN JONES, and K. DABER.

Asthma Clinic

The results of long-term treatment of chronic asthma with oral cortisone. R. S. SAVIDGE and W. BROCKBANK.

Department of Neurology

The effects of vitamin deficiency on the cerebrum, brain-stem, spinal cord, and peripheral nerves. F. R. FERGUSON, E. C. HUTCHINSON, and P. O. YATES.
Thrombosis of the internal carotid artery. G. E. SMYTH, E. C. HUTCHINSON, and P. O. YATES.
The effect of various substances on the duration of myotonia in dystrophia myotonica and myotonia congenita. L. A. LIVERSEDGE and M. NEWMAN.

The effects of pregnancy and trauma on the mode of presentation and subsequent development of angiomata of the spinal cord. L. A. LIVERSEDGE and E. C. HUTCHINSON.

Department of Child Health

Studies on pigment changes in kernicterus: associated dental changes and experimental production. R. M. FORRESTER, D. C. A. BEVIS, and J. MILLER.
Galactosaemia. A. HOLZEL, G. KOMROWER, and V. SCHWARTZ.
Tumours in children. J. K. STEWARD.

Department of Occupational Health

Byssinosis. R. S. F. SCHILLING and R. C. WOODCOCK.
Intervertebral-disk degeneration in relation to occupation. J. S. LAWRENCE.

Department of Clinical Pathology

The laboratory control of antibiotic therapy. R. W. FAIRBROTHER.

Department of Rheumatology

Differential diagnosis of ankylosing spondylitis. J. SHARP.
Generalized osteoarthritis. J. H. KELLGREN, J. BALL, and J. S. LAWRENCE.
The differential agglutination test in rheumatoid arthritis and other conditions. J. BALL.
Connective-tissue metabolism in experimental limb atrophy. H. G. B. SLACK.

Department of Surgery

Arteriograms illustrating the types of occlusive arterial disease. A. M. BOYD.

Department of Radiology

The radiological investigation of intracranial aneurysms. R. G. REID.
Arteriovenous fistulae of the lung. J. BROWN.
Some radiological manifestations of Hodgkin's disease. G. B. LOCKE.

University Medical Library

A collection of old, interesting, and amusing medical books. G. WILSON and W. BROCKBANK.

Annual Dinner

The Annual Dinner was held in the Whitworth Art Gallery, the local members kindly providing a sherry party beforehand. The President, PROFESSOR J. CHRIGHTON BRAMWELL, was in the chair. The toast of the Association was proposed by the President, and that of the guests by PROFESSOR ROBERT PLATT. SIR JOHN STOPFORD, Vice-Chancellor of Manchester University, replied. The toast of the President was proposed by DR. RAE GILCHRIST, and the President responded. MISS MARGARET PILKINGTON, Honorary Director of the Whitworth Art Gallery, gave a brief account of the collection of pictures, which members and their guests were then enabled to view.

Saturday, 9.30 a.m.

7. DR. R. ACHESON (introduced) and DR. ALICE STEWART, in their communication on *Bone Marks of Disease*, described those aspects of the Oxford Child Health Survey which were designed to discover the effects of childish ailments on growing bones. The data available comprised: (1) The annual incidence of illnesses other than head colds, and of Harris's lines, in the growing ends of long bones for 2,296 child years (representing the second, third, fourth, and fifth years of life of 650 children). (2) Annual increments of body-length and skeletal maturity (in Oxford units) for the same population. From statistical investigation of this material it was concluded that there was a definite inverse relationship between sickness exposure and increase in body-length, but not between sickness and increase in skeletal maturity. Thus the end-result of repeated illnesses in childhood might be a slight reduction in adult height. Further, a relationship was found between sickness experience and incidence of Harris's lines, which suggested that the latter marked the times of retarded skeletal growth.

DR. RUSSELL FRASER asked whether the less accurate correlation with bone age than with height might not be due to the less accurate method of measurement of the former, and whether the position of the lines had been related to the time of occurrence of the illnesses.

DR. P. HUGH-JONES (introduced) asked whether there was any evidence about the possible effects of rest in bed, apart from the illnesses, on the bone marks.

DR. E. G. L. BYWATERS inquired about the criteria used for the 'lines', since all gradations exist between faint, scarcely discernible striae and gross scars, such as those seen in Still's disease.

PROFESSOR A. V. NEALE asked if any specific influence upon growth hormone had been elicited in the 'general metabolic disorder' arising in the chronic infections related chronologically to the bone marking.

DR. W. C. SMALLWOOD asked whether the results obtained had been related to the social background, and in particular to the nutritional history, of the children.

Dr. R. E. SMITH said that bone marks occurred following infections in children from the upper social classes as frequently as in those from the lower classes. This applied particularly to the acute infectious diseases, commoner among children from the upper classes.

Replying, DR. ACHESON and DR. STEWART explained that the exact time of the occurrences of the lines had not been determined. The Oxford system of measuring skeletal maturity was still experimental, but was an advance on Todd's method. In reply to Dr. Bywaters, they explained that striae were only accepted when they were clearly visible in each tibia, fibula, and femur. Nothing equivalent to the bizarre markings of Still's disease had been seen. Some children had lines but no illnesses. A possible explanation of the lines was that they recorded a temporary disturbance of protein metabolism.

8. DR. B. E. C. NORDIN (introduced) and DR. RUSSELL FRASER, in their discussion of *Diagnostic Procedures in Osteomalacia*, described a bone biopsy needle with which adequate bone samples could be obtained from the iliac crest for histological examination. The whole procedure was done under local anaesthesia, and took about half an hour to perform. Sections of normal, osteoporotic, and osteomalacic bone were shown, to indicate that the sample provided ample material for diagnostic purposes. It was not suggested that bone biopsy should become a routine procedure; two biochemical tests were described which might also contribute to the diagnosis of osteomalacia. A calcium-infusion test, in which 15 mg. of calcium per kg. body weight was infused over four hours, had been carried out in 21 normal subjects, 20 patients with osteoporosis, and 12 with osteomalacia, all on a low-calcium diet. Normally in the first 12 hours after the beginning of the infusion 27 to 55 per cent. of the administered dose of calcium appeared in the urine over and above the 'basal excretion' calculated from the previous day's output. In osteomalacia the excretion was invariably 27 per cent. or less. In 17 cases of steatorrhoea, low excretion figures had been obtained in eight, and ancillary evidence suggested that these patients were suffering from early osteomalacia. The phosphate/creatinine clearance ratio could be of some diagnostic value, in that a high figure relative to the serum-phosphate level suggested primary and secondary hyperparathyroidism. Abnormally high figures had also been seen, however, in Cushing's syndrome and in a few cases of renal stone.

DR. S. W. STANBURY asked if bone biopsy had been done in the group of steatorrhoeic patients classified as 'candidates for osteomalacia' on the basis of the calcium-infusion test. He also pointed out that several factors other than excessive parathyroid function could cause increased renal phosphate clearance. Among these, acidosis was unlikely to complicate steatorrhoea, but potassium depletion was not uncommon and could also produce phosphaturia. A patient with gross depletion recently studied had a serum-phosphate level of 1·2 mg. per 100 ml. and a $C_P/C_{in.}$ ratio of 0·30; the serum-phosphate and the clearance ratio became normal with potassium repletion. There was no osteomalacia.

DR. J. D. NABARRO did not consider that these tests were practicable for the detection of osteomalacia of renal origin. He regarded iliac crest biopsy as most helpful, but doubted whether the calcium-infusion or phosphate-clearance tests were really worth while. The preliminary low-calcium diet used for the infusion test was often difficult to arrange, and the biochemical estimations were time-consuming. He questioned the accuracy of plasma-creatinine estimations performed by standard methods.

PROFESSOR J. H. KELLGREN stated that osteomalacia was, by definition, a morbid anatomical change, and could only be diagnosed with certainty by histological evidence. The importance of a bone biopsy studied by a competent bone pathologist could not be over-emphasized.

DR. D. K. O'DONOVAN referred to his experience of a calcium-retention test (which he had discussed at the Annual Meeting of the Association in 1947) using a smaller dose of calcium than that suggested by Dr. Nordin. He felt that the test was unsatisfactory because it gave little indication of the degree of osteomalacia; thus a minor calcium

deficiency might be included with osteomalacia. Another difficulty arose from false positive results which might rarely occur in osteoporosis. He said he was reluctant to give large doses of calcium intravenously to elderly patients or patients with heart disease, for he had seen unpleasant extrasystoles during calcium infusion, and abnormal electrocardiographic findings, and even sudden death, had been reported following intravenous calcium administration. He seldom used the test now.

In reply, DR. NORDIN said that in the past his bone biopsies had been decalcified before being stained, so that the results had been inconclusive. He agreed that a high clearance ratio was occasionally found in conditions other than hyperparathyroidism; he had already referred in particular to Cushing's syndrome. It was also true that the calcium-infusion tests and the phosphate/creatinine clearance ratio were of no diagnostic value in renal osteomalacia. The calcium-infusion test could be done on a ward diet restricted in dairy products so long as the diet was fairly consistent from day to day, but the results were invalid if the patient was having a high calcium intake. It was true that the estimation of plasma-creatinine had been unsatisfactory, but recent procedures were a great improvement. He had never seen cardiological complications during or after calcium infusion, and an electrocardiogram done on the only patient who vomited at the end of an infusion had been normal.

9. DR. J. BADENOCH, DR. J. R. EVANS, and DR. W. C. D. RICHARDS (introduced by PROFESSOR L. J. WITTS) reported the results of a study of *The Stomach in Hypochromic Anaemia*. Fifty patients with hypochromic anaemia had been studied. In all but five of these either a low intake of iron or chronic loss of blood could have accounted for the iron deficiency. A gastric biopsy had been carried out on each patient. The specimens showed variable histology, ranging from an almost normal appearance to severe gastritis and atrophy. In a few, atrophy of the body mucosa was extreme and was comparable to that found in pernicious anaemia. Severe changes in the gastric mucosa were more common in elderly patients with hypochromic anaemia, and in them atrophy was more prevalent than in normal persons of the same age. Good correlation had been found between the severity of the pathological changes in the gastric mucosa and the degree of impairment of gastric secretion. In 19 of the 20 patients with severe gastric atrophy, histamine-fast achlorhydria was present, and there was a great reduction in the gastric secretion of pepsin and the urinary excretion of uropepsin. In the few with extreme atrophy, studies with radioactive vitamin B_{12} had revealed some impairment of secretion of intrinsic factor. In patients with hypochromic anaemia, achlorhydria was twice as common at all ages and four times as common under the age of 50 than it was in normal controls. It was unlikely that this was due solely to anaemia, because Waldenström had found achlorhydria in patients with the mucosal changes of iron deficiency but without anaemia, and had shown that acid secretion returned after iron therapy. That iron deficiency might be responsible for the mucosal changes was suggested by the observation that the histological appearances could improve on iron therapy. Moreover, the incidence of glossitis, angular stomatitis, koilonychia, and dysphagia was much higher in patients with iron deficiency and gross gastric atrophy than it was in those in whom the stomach was normal or nearly so.

DR. A. R. KELSALL asked whether there was any correlation between mucosal atrophy and dyspeptic symptoms.

DR. J. M. NAISH asked whether low serum-B_{12} levels had been found in cases with atrophic gastritis, and whether the patients with the severest degree of gastritis showed more intolerance of iron than those without gastritis.

DR. A. C. DORNHORST asked whether there was any evidence of occult bleeding in the patients with severe gastritis.

DR. W. A. BOURNE pointed out that atrophic gastritis was not uncommon in cases without anaemia.

DR. W. WHITAKER inquired about the correlation between severity of mucosal change and degree of anaemia, and suggested that the gastric changes might be the result of a low visceral blood-flow, such as is found in the kidneys of patients with severe anaemia.

PROFESSOR A. V. NEALE reported that histamine-resistant achlorhydria was frequently found in simple iron-deficiency anaemia of children under 10 years of age, and that the gastric secretion returned to normal several weeks after successful iron treatment of the anaemia.

DR. BADENOCH replied that some of the patients complained of flatulent dyspepsia, but in none had it been a major complaint. He could not correlate its occurrence with severe gastritis. In two of the patients with gross gastric atrophy and impaired secretion of intrinsic factor, the levels of vitamin B_{12} in the serum had been within the range seen in

pernicious anaemia. The patients with severe gastritis had not appeared less tolerant of oral iron than those without gastritis. Many of the patients had occult bleeding, and in many this appeared to be a major cause of the iron deficiency. There was no evidence that it was more common in those with severe gastritis. He agreed that gastritis could be present without any defect in red-cell formation. Iron deficiency was only one of many factors producing lesions in the gastric mucosa.

10. Dr. R. H. Girdwood made *Some Observations on the Megaloblastic Anaemias and their Diagnosis*. When the clinical problem in anaemia was complex, assistance in diagnosis could be provided by serum-vitamin-B_{12} estimations, by measurement of folic-acid absorption (by estimating its output in the urine after injected and oral test doses), and from studies with labelled cyanocobalamin. The first two tests involved technically difficult microbiological assays. In 60 cases of untreated pernicious anaemia the serum-vitamin-B_{12} level had only twice exceeded 120 $\mu\mu$g. per ml., whereas in 120 controls it had ranged from 130 to 750 $\mu\mu$g. per ml. (mean 299·9 $\mu\mu$g. per ml.), with *L. leichmannii* as test organism. In all of 28 cases of idiopathic steatorrhoea and related conditions shown to have had intestinal malabsorption by other means, there had been malabsorption of folic acid, even in the absence of anaemia. The serum-vitamin-B_{12} level had been low in one such case. In six out of seven cases of active coeliac disease, none of whom had megaloblastic anaemia, there had been malabsorption of folic acid. This folic-acid test involved only two 24-hour urine collections. Routine fat-balance tests might give misleading results. Where steatorrhoea had occurred after gastric operations or fistulae, the test had not shown malabsorption of folic acid, but a low serum-vitamin-B_{12} level might develop and might precede megaloblastic changes. In the 12 cases of megaloblastic anaemia of pregnancy investigated there had been no evidence of malabsorption of folic acid, and in 14 such cases the serum-vitamin-B_{12} level had been normal. In developing pernicious anaemia a low serum-vitamin-B_{12} level might precede obvious megaloblastic change by several months: glossitis and neurological features might precede megaloblastic anaemia.

Dr. C. L. Cope asked how the folic-acid excretion test compared with the reticulocyte response to oral folic acid in these patients, and whether the former test provided additional information.

Dr. Girdwood replied that many of the patients with intestinal malabsorptive diseases of the sprue type had had folic-acid therapy for some time before the differential urinary folic-acid excretion test was done; others had no anaemia or iron-deficiency anaemia, so that there was no relationship between reticulocyte response and the results of this test. It was perhaps surprising that there was a haemopoietic response to oral folic acid therapy in patients who were shown to absorb folic acid poorly, but there was always some absorption of folic acid. Nevertheless, in certain cases of idiopathic steatorrhoea this absorption was so poor that it was advisable to give injections of folic acid at the start of treatment and, since malabsorption of vitamin B_{12} might also occur, to supplement the folic acid with monthly injections of cyanocobalamin. It was possible that folic acid therapy improved the absorption of folic acid itself.

11. Dr. A. J. Buller (introduced) and Dr. A. C. Dornhorst, in a discussion of *Sound Transmission through the Chest*, described how they obtained the objective equivalent of certain physical signs of chest disorder. Pure tones from a loud-speaker were led through a mouthpiece into the subject's airways, and the transmitted sounds picked up by a microphone on the chest wall. In this way the spectrum of sound-transmission had been mapped in normal subjects and patients with abnormal signs such as bronchial breathing. Examples of normal transmission and of modifications giving rise to various signs were shown. It was hoped that the method would lead to better definition of the circumstances in which the signs occurred, and would assist in teaching.

Professor Crighton Bramwell emphasized the clinical importance of these observations, and pointed out that the 'loudness' of sounds heard by auscultation depended on their intensity, as modified by the sensitivity of the perceptive mechanism, the human ear being much less sensitive to sounds of low pitch than to those of a moderately high pitch.

Dr. C. L. Cope asked whether the higher-pitched breath sounds heard near the top of a pleural effusion were considered to be due solely to preferential absorption of lower wavelengths of sound by the fluid, rather than to compression of lung tissue by the fluid as had been thought in the past.

Dr. J. G. Scadding inquired whether the results were affected by resonances in the mouthpiece and upper air passage, and whether the small peak at 800 cycles per second in the curve of transmission of sound through a pneumothorax corresponded to the natural resonance of the hemithorax.

DR. C. M. FLETCHER wondered whether some part of normal breath sounds did not originate within the lung rather than at the larynx, so that they were subject to conditions of transmission different from those studied in these experiments.

DR. T. E. GUMPERT expressed his interest in the transmission of sound through fluid, and felt that the difficulty was not in large pleural effusions, where bronchial breathing might well be heard, but in smaller effusions where neither physical signs nor X-ray findings might be entirely diagnostic. He thought tactile vocal fremitus was one of the most reliable signs of fluid in the chest.

DR. R. E. SMITH said that the opinions of house physicians trained in different medical schools suggested that water was a good conductor of sound in some places and a bad one in others. He asked if Dr. Dornhorst agreed that the greater elasticity of the lung in young patients allowed full collapse of the lung underlying the pleural effusions, whereas sounds were not transmitted through the partially collapsed lung and the fluid in older patients.

In reply, DR. DORNHORST agreed with Professor Bramwell that a correction for the variation of aural sensitivity with pitch was needed before the results could be interpreted in terms of loudness. This was particularly important at the lower frequencies. It was fairly easy to make sure that the apparatus had no resonances in the range used. Resonances of the upper air passages undoubtedly existed, but did not appear to influence the records. He thought that transmitted sounds were responsible for most abnormal types of breathing, but did not deny that the normal breath sounds contained elements of local origin. More data on pleural effusion were needed before all the points raised could be answered. In the total effusion described there was an absolute increase in high-frequency transmission: in smaller effusions high-pitched breath sounds were more likely to be due to selective loss of the lower frequencies.

12. DR. D. W. BARRITT (introduced by PROFESSOR C. BRUCE PERRY) described work upon *Visible Lipaemia after a Fatty Meal in Coronary Artery Disease*. After a fatty meal the presence of large fat particles caused turbidity of the serum. The intensity of the serum turbidity which followed the ingestion of fat had been measured in 20 men who had recently had a myocardial infarction, and in controls. A standard meal of 60 gm. of milk fat was given, and the visible lipaemia of the serum was measured in a spectrophotometer at 680 mμ before, and three, five, and seven hours after the meal. Of 21 male control subjects of the same age-group as the coronary series, 19 showed a peak of lipaemia at three hours which had virtually cleared at seven hours. In two the peak was at five hours, and in these two there was failure to clear by seven hours. The intensity of the lipaemia at its peak varied very widely. In the coronary series the same wide variation was found. There was a much stronger tendency for the peak to occur at five hours than in the control series, and failure to clear by seven hours occurred seven times. The difference between the two groups at seven hours was statistically significant. Fourteen pre-menopausal women were submitted to the same test. None failed to clear by seven hours, and the three-hour peak was at a lower level than in the other two groups. The results appeared to imply a relationship between coronary artery disease and slowness in clearing large fat particles from the blood.

PROFESSOR CRIGHTON BRAMWELL commented upon the relevance of these observations to the influence of diet upon coronary disease.

DR. K. W. DONALD said that he felt unhappy about the use of the term 'peak values' to describe the first observations made after the fatty meal. The curves shown all suggested that lipaemia was considerably greater in both normal and diseased subjects during the period between the meal and the first observation. He would suggest that more detailed study of the behaviour in the early period might be rewarding and might show important differences between the normal subjects and the patients.

DR. RUSSELL FRASER asked whether the abnormalities might not correlate better with obesity.

DR. C. L. COPE wondered whether the control group was a valid one, and whether changes in the lipaemia curve could result merely from long rest in bed or other non-specific causes.

DR. R. I. S. BAYLISS asked how repeatable the results were. If the test was repeated on alternate days, was the same degree of lipaemia induced on each occasion, and did the lipaemia last for the same length of time?

DR. S. P. ASPER (introduced) stated that the occurrence of anginal pain several hours after a fatty meal had been reported, and asked whether any of the patients in the series had been similarly affected.

In reply, DR. BARRITT said that no samples had been taken less than three hours after the meal. No relationship had been found between obesity and prolonged lipaemia. Rest in bed was not thought to be an important factor; many of the control subjects had been in bed after operations, and the tests of those coronary patients who were investigated when ambulant gave results similar to those in patients still confined to bed. Repeated tests usually showed a similarly shaped curve in the same patient, but the intensity of the lipaemia might vary considerably. No patient had complained of chest pain after the meal.

13. DR. K. P. BALL, PROFESSOR C. V. HARRISON (introduced), and DR. J. F. GOODWIN described the clinical and pathological features in two cases of *Thrombosis of the Large Pulmonary Arteries* diagnosed during life. The essential features were progressive dyspnoea, syncopal attacks, and peripheral venous thromboses. There were congestive heart failure, enlargement of the right ventricle, and a systolic murmur over the pulmonary artery with a normal pulmonary element of the second heart sound. Fluoroscopy showed enlarged and poorly pulsatile main pulmonary arteries with clear lung fields. Analysis of over 6,000 autopsy records had revealed a further 19 cases, in 17 of which there was associated cardiovascular, pulmonary, or gastrointestinal disease. Five of these patients had had mitral stenosis, which was thought particularly to favour the occurrence of thrombosis of the pulmonary artery *in situ* because of underlying local disease, pulmonary hypertension, and low cardiac output. In seven of the 21 cases described there had been pathological evidence which suggested thromboses *in situ* rather than embolism. The authors considered that the diagnosis of pulmonary artery thrombosis should be considered in any case of obscure congestive heart failure, especially when accompanied by peripheral venous thrombosis, and also in patients with mitral stenosis who developed unexplained fainting attacks and right ventricular failure with diminishing pulsation of the main pulmonary arteries. Prolonged anticoagulant therapy might prevent a fatal outcome if instituted in time.

PROFESSOR C. STUART-HARRIS asked whether the recognition of the condition of thrombosis of the pulmonary artery was aided by reference to dyspnoea. In two personal cases encountered recently in Sheffield an exceptional degree of dyspnoea had been observed. The first case occurred in a patient with chronic right heart failure secondary to pulmonary sarcoidosis, and the second in a woman with thrombocytosis following splenectomy for haemolytic anaemia.

In reply DR. GOODWIN said that sudden attacks of breathlessness were a feature in the first patient described, but were sometimes noted in association with episodes of supraventricular tachycardia. Such sudden attacks of dyspnoea were, however, probably a valuable pointer to the diagnosis.

14. DR. M. G. FITZGERALD (introduced) and DR. PAUL FOURMAN described the *Production of an Alkalosis in a Potassium Deficiency, and its Correction with an Alkaline Salt of Potassium*. The alkalosis of uncomplicated potassium deficiency had been attributed in part to the movement of hydrogen ions into cells, leaving the extracellular fluid more alkaline than normal, but it was not clear in what way the kidneys maintained the alkalosis. The question had been investigated in a woman with base-losing nephritis which had produced both potassium deficiency and acidosis. The patient had first been allowed to lose 350 mEq. of potassium. Sodium bicarbonate added to her diet in a dose of 360 mEq. daily for three days produced a severe extracellular alkalosis and some fluid retention, and she had gained 780 mEq. of sodium, but without any gain of chloride. Potassium bicarbonate in addition to the sodium bicarbonate produced a rapid relief of the symptoms of alkalosis, with a retention of chloride and loss of sodium. The experiment showed that during a potassium deficiency the renal tubules did not respond normally to an alkalosis. Dr. Fitzgerald emphasized the dangers of giving free doses of alkali to patients who had a deficiency of potassium.

DR. D. A. K. BLACK suggested that these observations were open to the criticism that the renal-tubule cells in this patient were abnormal, so that their behaviour did not necessarily represent a normal reaction. It was therefore pertinent to note that a similar correction of hypokalaemic alkalosis by alkaline salts of potassium had been observed in potassium-depleted normal rats, and also in patients with potassium depletion secondary to pyloric stenosis.

DR. M. D. MILNE considered that these observations had further elucidated the defects in renal control of acid-base balance imposed by potassium deficiency. In severe acidosis the kidney in potassium deficiency was unable to exchange a sufficient amount of hydrogen ion to produce a maximally acid urine. Conversely, in severe alkalosis, there was inefficiency in the limitation of hydrogen ion exchange, with the result that bicarbonate excretion was subnormal.

PROFESSOR R. PLATT asked what was the glomerular filtration rate as estimated by inulin or creatinine, and what was the proportion of filtered sodium reabsorbed by the tubules at different stages of the investigation.

IN reply DR. FITZGERALD stressed the fact that, although the patient's kidneys were abnormal, they had been fully able to excrete the sodium bicarbonate when the potassium deficiency had been corrected. The glomerular filtration rate, measured by the endogenous excretion of creatinine, was 76 ml. per minute, 74 ml. per minute, and 71 ml. per minute in the three periods of the experiment. The percentage of sodium apparently reabsorbed by the tubules was the same in the first and second periods, but fell in the third.

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